Preoperative Progressive Explosive-Type Resistance Training in Patients with Hip Osteoarthritis scheduled for Total Hip Arthroplasty

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1. Preface

The thesis was accomplished at the Institute of Clinical Research, Faculty of Health, University of Southern Denmark.

Main supervisor was Professor Søren Overgaard, The Orthopaedic Research Unit, Department of Orthopaedic Surgery and Traumatology, Odense University Hospital.

Co-supervisors were; Anders Holsgaard-Larsen, The Orthopaedic Research Unit, Department of Orthopaedic Surgery and Traumatology, Odense University Hospital, Bo Zerahn, Department of Clinical Physiology and Nuclear Medicine, Herlev University Hospital and Steen Mejdahl, Department of Orthopaedic Surgery, Herlev University Hospital.

The thesis is based on three studies conducted at The Department of Orthopaedic Surgery and Traumatology, Odense University Hospital (Study 1) and The Department of Orthopaedic Surgery, Herlev University Hospital (Study 2 & 3) between 2010 and 2013.

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2. Content

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4. List of papers

Hermann A, Ried-Larsen M, Jensen AK, Holst R, Andersen LB, Overgaard S, Holsgaard-Larsen A. Low validity of the Sensewear Pro 3 activity monitor compared to indirect calorimetry during simulated free living in patients with osteoarthritis of the hip. BMC Musculoskeletal Disorders *2014, **15**:43*

Hermann A, Holsgaard-Larsen A, Zerahn B, Mejdahl S, Overgaard S. Feasibility and effects of preoperative progressive explosive resistance training in patients with hip osteoarthritis scheduled for total hip arthroplasty - a randomized controlled trial

Hermann A, Zerahn B, Mejdahl S, Overgaard S, Holsgaard-Larsen A. Changes in isometric muscle strength, physical functioning and body composition following preoperative resistance training – an explorative randomized study in patients scheduled for THA.

5. Abbreviations

ADL: Activities of daily living

ANOVA: Analysis of variance

BMI: Body mass index

CG: Control group

CI: Confidence interval

CONSORT: Consolidated standards of reporting trials

CONTENT: Consensus on therapeutic exercise and training

CT: Computer tomography

CV: Coefficient of variance

MR: Magnetic resonance

DXA: Dual-energy X-ray Absorptiometry

GI: Gastrointestinal

HOOS: Hip dysfunction and Osteoarthritis Outcome Score

ICC: Intraclass correlation coefficient

MVC: Maximal voluntary contraction

NSAID: Non-steroidal anti-inflammatory drugs

OA: Osteoarthritis

RCT: Randomized clinical trial

RFD: Rate of force development

RT: Resistance training

SMD: Standardized mean difference

THA: Total hip arthroplasty

VAS: Visual analog scaleWOMAC: Western Ontario and McMaster Universities Arthritis Index

6. Introduction

6.1 Hip OA

6.1.1 Pathology and definitions

Osteoarthritis (OA) is a common degenerative disorder affecting synovial joints. Pathologically, the key feature regardless of location is the progressive damage of the cartilage of the articulating surfaces [1,2].

The clinical diagnosis of hip OA is based on the history of symptoms supplemented by physical findings and is confirmed by plain radiographs[3]. The cardinal symptom of hip OA is joint pain initially associated with activity and relieved by rest. With progressive disease, pain may become more constant and eventually disturb sleep[4]. Joint degeneration can lead to joint stiffness and reduced range of motion as reported by the patient or observed by clinical examination[5].

Impaired physical functioning might lead to deterioration of muscle function in progressive disease and eventually affect the activity level in daily living as discussed in later sections. Worsening of symptoms may also affect quality of life as well as work participation[6].

OA is commonly classified in two main subgroups; primary (idiopathic) OA, in which no prior event or disease is related to the OA; and secondary, in which a known associated event or disease is related to OA (e.g. previous fracture, congenital disease, bone dysplasia etc.)[7].

6.1.2 Etiology, epidemiology and impact in society

The etiology of primary OA remains a challenge mainly due to a heterogenic pathogenesis that is far from being disclosed. Both biomechanical and inflammatory factors are believed to be important in the development of joint lesions in primary OA and a strong genetic predisposition seems to interplay as well [8–10]. Despite being a common disorder, estimation of the prevalence is limited by inconsistency between studies in the criteria for reporting OA (self reported, symptomatic or radiographic). In a recent systematic review based on 28 studies an overall prevalence of hip OA of 10.9% was reported; with the estimated average prevalence ranging between 6.1% and 15.1% depending on the criteria for reporting OA, with radiographic OA being most frequent [11]. Furthermore, the prevalence of hip OA is strongly associated with age[4,12].

Currently, OA is without cure and the general burden on society is immense[13]. OA is rated among the most common causes of disability related to musculoskeletal disorders and with a growing population of elderly the socioeconomic impact on society is likely to increase[14]. For the US population the total socioeconomic burden of OA has been estimated to US$ 89 billion per year which include direct medical costs and indirect costs related to lost wages, lost productivity, home care etcetera[15]. Predictions regarding primary hip replacements indicate a 174% increase by 2030 while demands for revisions will be doubled (US figures) [14] which will affect the future development in both direct medical costs and indirect costs.

6.1.3 The management of hip OA

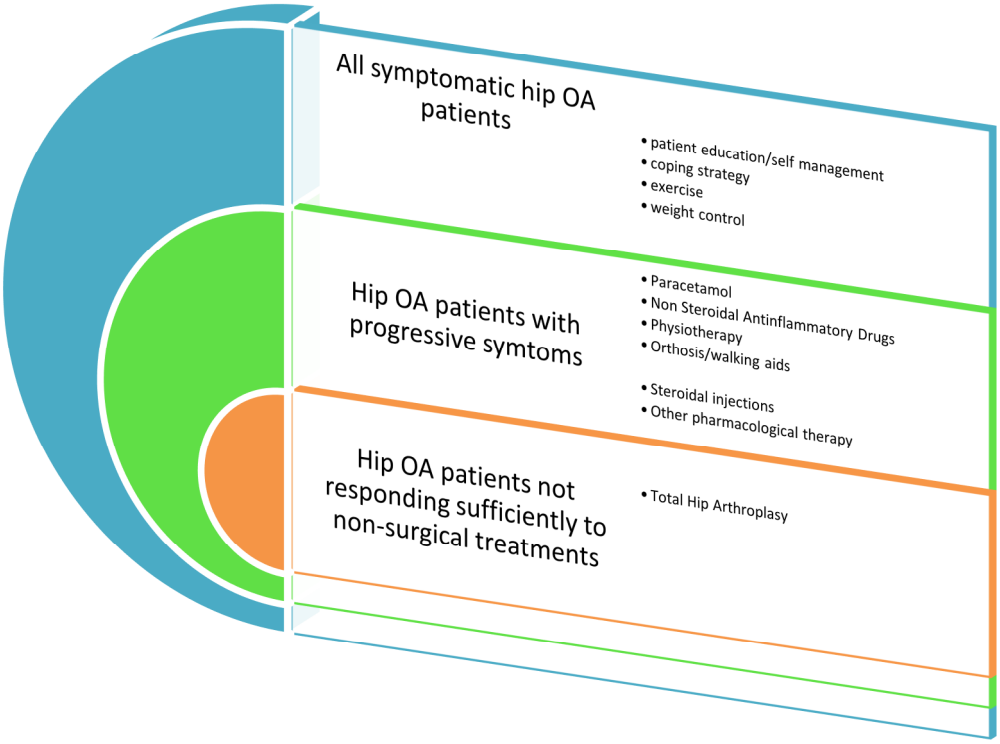
Interventions are mainly targeting the following areas: Pain relief, preservation of physical functioning or improving disability, improving health related quality of life, limiting the progression of joint damage and promoting patient education related to self-management and coping strategy.

A three stage treatment strategy is commonly applied in hip OA[16]. In early stages, intervention strategies are based on treatments with a non-pharmacological approach (first line) with the addition of pharmacological (second line) and surgical treatments (third line) when needed [17,18]. Non-pharmacological interventions refer to any non-surgical treatment without involvement of medication and may include patient education related to self management and coping strategy, weight loss (when indicated) and exercise therapy; however the efficacy on pain and function is generally not as well established in hip OA as for knee OA[17]. For hip OA patients with progressive symptoms without a sufficient respond to the initial treatment modalities, radical treatment with joint replacement surgery is indicated (figure 1).

Figure 1

A scope of common treatment strategy in hip OA based on the current OARSI recommendations*

*)W. Zhang, R. W. Moskowitz, Nuki M.B. et al. *OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis and Cartilage (2008) 16, 137-162.*



The THA is generally considered a reliable and suitable treatment for pain reduction and restoring of function in severe hip OA [19] and is recommended as the standard surgical procedure when non-surgical treatments fail[17]. The efficacy of THA related to improvements in health related quality of life outcomes are primary based on observational studies of uncontrolled cohorts[20]. In a systematic review including 74 studies (THA and/or TKA), Ethgen et al (2004) reported substantial improvements regarding pain and physical function following total joint replacement surgery[20].

Throughout the century the THA has developed into the most successful prosthetic procedure of orthopedic surgery and with more than a million procedures (estimated figures) currently being performed each year world wide [21,22]. Currently, close to 7000 primary THA procedures (based on the diagnosis primary hip OA) are performed annually in Denmark (2012 figures) and the incidence of THA procedures have more than doubled from 1995 to present [23]. However, it is an

important notion that a more than one quarter of THA patients report persistent pain in various degrees after THA [24] and a full recovery of physical functioning to a pre disease state, should not be expected [25]. The latter stresses the importance of alignment of the expectations of the patient and the surgeon before planning of surgery.

6.2 Hip OA; impact on muscle and physical functioning

Besides pain, impaired physical functioning is the cardinal symptom affecting hip OA patients[26]. Typically, the functional impairments in lower extremity OA affect walking activities and strenuous motor tasks such as stair climbing or rising from chairs[27,28], which is essential for independence in daily living. Importantly, impaired preoperative physical function and muscle (quadriceps) capacity have been identified as predictors of poor functional outcome after THA[29,30]. The identification physiologic factors involved in the functional deterioration observed in hip OA patients is important since it may serve as a target for improvement of current management strategies for a better post-operative outcome.

In hip OA, functioning is a commonly evaluated in terms of activities of daily living (ADL) using a patient reported outcome measure like the Oxford Hip Score, the Western Ontario and McMaster Universities Arthritis Index (WOMAC) or Hip dysfunction and Osteoarthritis Outcome Score (HOOS). Regarding the course of decline in ADL function, existing studies indicate hip OA to be a stable condition for the majority of patients even in a severe symptom state[31–33]. Still, considerable variation is observed on the individual level [32,33]. Several factors have been identified as predictors of accelerated functional deterioration, including avoidance of activity, increased pain, co-morbidity, reduced ROM, and higher age [32,33].

Age related changes in muscle function

Since the prevalence of hip OA is strongly associated with age many patients will also be affected by general age related physiologic changes that may affect treatment and rehabilitation strategy. Impairment of functional performance and mechanical muscle function is associated in healthy elderly [34]. With increasing age a marked decline in neuromuscular function is observed, mainly due to a reduction in total number of motor neurons [35]. As a consequence, contractile muscle fiber characteristics are affected according to both their cross sectional size (atrophy) and numbers (hypoplasia), especially for fast twitch (type II) fibers[35,36]. These changes eventually affect mechanical muscle functions through impairment of maximal muscle strength. In particular the explosive strength characteristics (the rate of force development) and muscle power (the product of muscle force/torque and velocity of movement) which both appear to decline earlier and faster than maximal muscle strength[35].

Eventually physical functioning is affected since, the leg muscle power is observed to correlate to impaired functional capacity regarding common ADL tasks like walking, stair climb and chair rise [34,37].

Changes in muscle function in relation to hip OA

In hip OA patients, the deterioration of leg muscle function has clinical importance as a predictor for poor functional outcome after THA [29,30]. This indicates that preservation or restoration of the preoperative leg muscle function may be important for the rehabilitation of ADL function after THA.

According to a resent meta-analysis by Loureiro et al (2013), the greatest reductions in strength are found for the hip and knee flexors and extensor groups[38]. The meta analysis identified 13 studies in hip OA patients of which 8 studies compared affected leg with unaffected contra-lateral leg, while 5 studies compared hip OA patients with healthy controls[38]. For hip adductors and hip abductors findings are less consistent[38–41], however, two studies identified affected hip abductor strength in hip OA patients compared to healthy controls [39,42]. For hip OA patients undergoing hip replacement surgery the loss of muscle strength is sustained after surgery which may affect recovery of ADL functions after THA [25,41,43].

As previously described muscle atrophy and/or hypoplasia is commonly related to impairments of muscle strength[35]. For hip OA patients general muscle atrophy in the affected leg compared with the contra lateral leg has been observed, providing strong evidence for a reduced quadriceps muscle size[38]. Unfortunately, evidence of the actual course of deterioration of muscle strength and muscle size in hip OA is sparse, since the current literature is limited to cross sectional studies[38].

These findings indicate that interventions targeted the preservation of leg muscle function may have clinical importance for hip OA patients, and for patients scheduled for THA in particular.

6.3 Hip OA and physical activity.

Treatment strategies in OA mainly focus on the core symptoms 'pain' and 'function', which may also affect physical activity levels. The functional impairment and pain related with OA might lead to a more sedentary lifestyle with increased risk of co-mobidity and mortality[44], which may be prevented through interventions improving physical functioning. However, evidence regarding physical activity and treatment effects in hip OA is sparse and conclusions are currently restricted by the lack of a valid objective physical activity measures in the hip OA population.

For older adults the American College of Sports Medicine recommends moderate-intensity activities of 30 or up to 60 minutes/day in bouts of at least 10 min each to total 150–300 minutes pr. week, with at least 20–30 minutes/day of vigorous activities[45]. According to two resent meta-analysis, the physical activity in populations with lower extremity OA have been estimated using various outcomes [4446]. Naal et al (2010) concluded that physical activity in people undergoing joint arthroplasty is below recommendations [44]. In the latest meta-analysis Wallis et al (2013) included 27 studies with objectively estimated physical activity in patients with lower extremity OA[46]. For hip OA they concluded low quality evidence that 58% of hip OA patients met physical activity guidelines of at least 150 min of moderate to vigorous physical activity per week.

These findings suggest that a large proportion of patients with lower extremity OA (including hip OA) do not meet recommendations regarding physical activity in daily living; however, the same is also evident for the elderly population in general[47] . Only little evidence exists regarding the actual physical activity level in patients with symptomatic hip OA in comparison to age matched healthy subjects. de Groot et al (2008) reported that 'motion related physical activity' was 11% lower in

patients with hip OA compared to healthy controls[48]. In comparison, Holsgaard-Larsen et al (2012) were unable to detect significant difference between lower extremity OA patients (hip and knee) and healthy controls according to physical activity based on estimates by a multi sensory activity monitor [49]. However, Holsgaard-Larsen et al (2012) also reported low agreement between simultaneous measured step count and physical activity estimates[49] indicating that precautions should be taken regarding interpretation and comparison of different physical activity measures.

At the time of the planning of the current RCT study the validity of objectively measured physical activity had yet to be established in hip OA patients, thus a population specific validation study of an objective physical activity outcome measure was highly warranted.

6.4 Preoperative exercise interventions on postoperative outcome and rehabilitation.

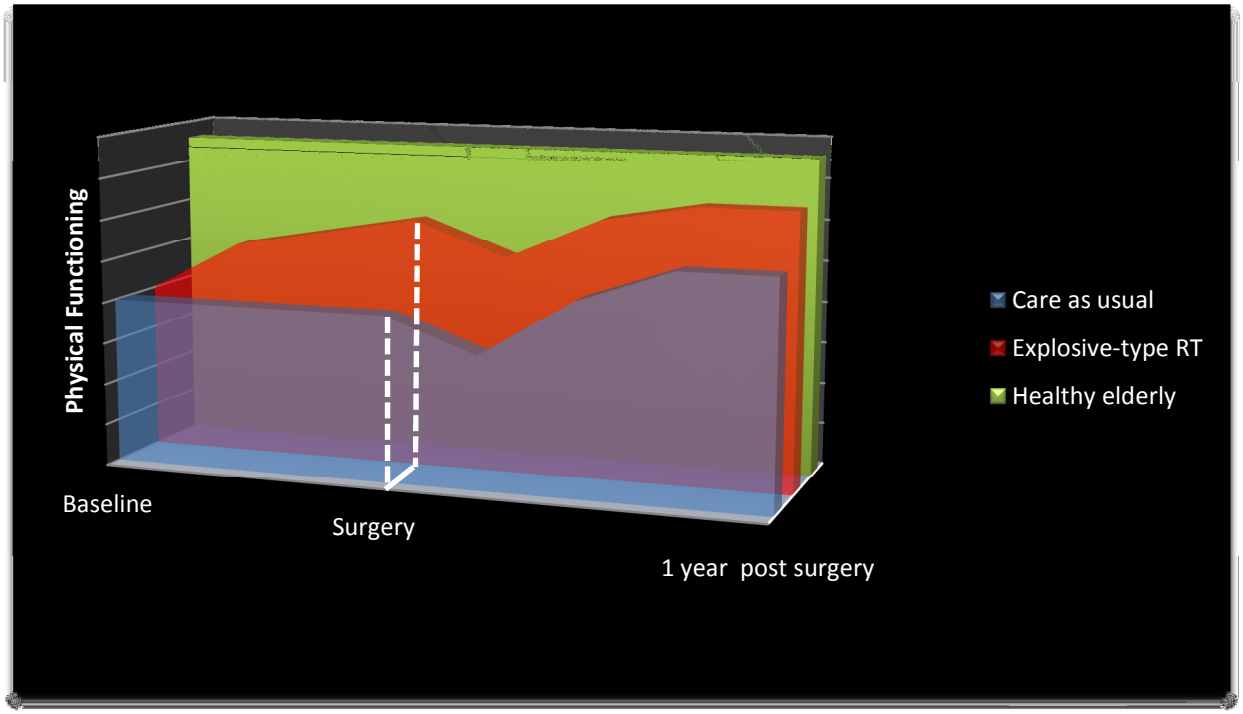
In relation to THA, rehabilitation traditionally defines a post-surgical intervention to improve post-operative mobilization and the recovery of functional capacity. Early mobilization is considered a crucial part of modern post-surgical management and the accelerated clinical pathways inspired by fast track surgery is becoming broadly adapted in daily clinic[50,51]. According to a recent meta analysis, recovery after THA remains a challenge since progression in post-operative physical function is reported to reach steady state after 6 to 8 months and stay below the pre-disease state[25]. Still, limited evidence exists on the efficacy of the physical therapy commonly applied after THA[52]. Following the multimodal approach applied in modern accelerated pathway surgery there is increasing interest of optimized and evidence based rehabilitation programs that recommend the optimal content of intervention and time in relation to surgery to improve early and late rehabilitation[53].

Suetta et al (2004) reported a significant additional loss of muscle strength and muscle size compared to the preoperative stage during the early (5 weeks) postoperative rehabilitation (standard physiotherapy) after THA[54]. Therefore, postponing the initialization of rehabilitation until after surgery may not benefit the early stages in postoperative mobilization since a certain time is to be expected before training induced physiological adaptations (in terms of augmentation of neuromuscular functioning) is attained [55]. In addition, improvements in preoperative predictors i.e.

impaired function and muscle function[29,30] may translate into earlier recovery and improved postoperative outcome[56,57] (see Figure 2).

Figure 2

The theoretical pre and post operative effect of preoperative explosive-type RT on physical function compared to care as usual and healthy elderly. The improvement of the physical function prior to surgery by enhancement of leg muscle function may create a shift of the course of postoperative function towards an improved postoperative outcome.



However, only a limited number of exercise studies have been conducted in relation to hip OA. A resent meta-analysis by Gill et al (2013) focusing on the effect of preoperative 'exercise therapy' in patients scheduled for total joint replacement was only able to indentify 7 studies of hip OA patients with large heterogeneity according to the content of intervention[58]. The authors found medium size effect on pain and self-reported function (SMD 0.45; 95% CI 0.15 to 0.75 and SMD 0.46; 95%CI 0.20 to 0.72, respectively) but no significant effect on either muscle strength or physical functioning (walking speed) was found[58]. Regarding the *postoperative* effects of preoperative 'exercise therapy' (broadly defined); Wallis et al 2011 reported moderate quality evidence that pre-operative exercise and education programs improve function 3 weeks after hip replacement[59], however this conclusion

was not shared by a later review by Hoogeboom et al (2012) who concluded no beneficial postoperative effect of preoperative therapeutic exercise[60]. None of the meta-analysis did however differentiate between contents of interventions. Since then, a resent high quality RCT (Villadsen et al 2013) investigating the postoperative effect of 8 weeks of preoperative neuromuscular exercise (mixed intervention) have reported a significant short term benefit according to function and pain but no sustained effect 3 months after surgery[57].

In their review, Hoogeboom et al identified general problems in the therapeutic validity of intervention, particular according to low documentation of intensity and progression of the exercise programs, which may have influenced the result of the meta analysis [60]. Similar considerations regarding insufficient intensity of interventions were raised by Gill et al (2013)[58]. This was recently supported by a systematic review of progressive resistance training (RT) in relation to joint replacement surgery that was only able to identify a single RCT with progressive RT included in the intervention[61]. This study indicated that progressive RT did improve post-operative physical functioning, however since the intervention group received progressive RT both before and after surgery it was not possible to determine the postoperative effect of the preoperative part of the intervention[62,63]

6.5 Progressive explosive-type resistance training

In order to improve or accelerated the functional outcome after THA, preoperative intervention with progressive resistance training might be important[61].

It is well established that progressive resistance training (RT) is highly effective in enhancing muscle strength and improving functional capacity in healthy elderly [64–69] within a typical intervention period of 8 to 12 weeks[70].

Due to its relevance for ADL tasks and risk of fall among elderly[34,71,72] the focus of RT interventions have shifted from improving maximal muscle strength towards maximal muscle power[73,74]. Thus, to improve ADL function, exercises enhancing muscle power rather than muscle strength is now recommended[34,75–77]. Intervention with explosive-type RT (RT exercises with maximal intentional acceleration of the load through the concentric phase) is reported to increase muscle power compared to conventional progressive RT in healthy elderly[65,69] and improve strenuous elements of ADL functioning[76]. Importantly, interventions with explosive RT is well tolerated and effective in both elderly and very old individuals indicating frailty not to be a contraindication [77].

Progressive explosive-type RT in hip OA

The neuromuscular deficits described in hip OA may accentuate the course of neuromuscular and functional decline present in the general elderly population with the risk of poor functional outcome for patients undergoing surgery[29,30]. Despite well established evidence for the efficacy of progressive medium to high intensity RT in healthy elderly, only limited evidence exist regarding the effect of this intervention in hip OA patients.

Four studies of preoperative exercise therapy in hip OA included 'strengthening exercises' as an adjunct to various types of aerobic exercises. Only one RCT (Gilbey et al 2003, Wang et al 2002) included progressive RT according to the physiologic principles of progressive overload, however; the RT exercises were performed at low velocity and mixed with aerobic exercises. Since the intervention group received the intervention both before and after surgery the efficacy of the

preoperative RT component was difficult to determine [62,63]. Importantly, none of the four studies exclusively investigated progressive RT provided prior to surgery.

All studies except one (Gilbey et al 2003) failed to find support for any effects on leg muscle strength prior to surgery and none of the studies found effect on objectively measured physical function before THA[58,62,63,78,79].

In hip OA patients, explosive-type RT have exclusively been investigated as a post-operative intervention[54,80–82]. Suetta et al (2004) reported explosive-type RT to be superior to conventional physiotherapy and neuromuscular electrical stimulation in the early rehabilitation phase, according to maximal muscle strength, explosive force characteristics (RFD) and functional tasks [54]. Additionally, increased muscle cross sectional areal and hypertrophy at muscle fiber level were reported. However, efficacy regarding patient reported outcomes on ADL function was not included and long term effect was not evaluated. Despite these findings, the efficacy of explosive-type RT as a preoperative intervention on hip OA patients remains unknown.

The motivation for this PhD-thesis was therefore to investigate if explosive-type RT was feasible and effective as a preoperative intervention to improve physical function in patients with end stage hip OA scheduled for THA.

6.6 Aims of the dissertation

The dissertation is based on 3 papers with the overall aim to evaluate preoperative progressive explosive-type RT in hip OA patients scheduled for THA.

The specific aims:

- To investigate the feasibility of a preoperative progressive explosive-type RT exercise program in hip OA patients scheduled for THA in terms of adherence, exercise related pain, drop-outs and adverse events (Paper II)
- To evaluate the efficacy of the intervention on self-evaluated ADL function, as primary outcome and self-evaluated pain/symptoms/sports and recreational function and hip related quality of life in addition to leg extension power as secondary outcomes compared to care-as-usual (Paper II)
- To investigate the effect of preoperative explosive-type RT on maximal muscle strength and body composition (fat free mass) (Paper II)
- To investigate the possible associations between changes in muscle function and changes in physical ADL functions and body composition following the intervention with preoperative explosive-type RT for the identification of possible muscle determinants for improvement in physical functioning in hip OA patients scheduled for THA (Paper III)
- To describe the reliability and agreement of muscle function tests and physical performance measures in hip OA patients scheduled for THA and to evaluate the validity of an objective surrogate measure of physical activity in patients with hip OA (Paper I, II and III)

6.7 Hypothesis

Based on the present evidence regarding efficacy of explosive-type RT in elderly and performed as post-operative rehabilitation in hip OA patients, it was hypothesized that:

- a preoperative intervention program consisting of 10 weeks of progressive explosive-type RT would be feasible in patients with hip OA scheduled for THA
- the intervention would be efficient to improve self-reported ADL function, physical performance and muscle function and increase fat free mass compared to care as usual.

Since this hypothesis was based on a theoretical causality between RT induced improvements of muscle function and better physical performance in hip OA patients; it was additionally hypothesized that:

- an association exists between improvements in muscle function and physical performance following intervention.

Finally, it was hypothesized that valid estimates of physical activity would be possible in hip OA patients, by the use of a commercial available activity monitor, in order to measure the potential efficacy of preoperative physical intervention regarding pre- and postoperative physical activity in future trials.

7 Presentation of studies; Methodology and Results

7.1 Methodological considerations

7.1.1 Study design

To answer the above mentioned aims regarding efficacy of preoperative explosive-type RT a RCT study design was selected. The study contributes to a high level of evidence, as the gold standard in studying health care interventions[83] and allows results from similar trials to be included in a meta-analysis to establish a high level of evidence. The RCT was designed, and data presented according to the principles of the CONSORT (Consolidated standards of reporting trials) statement and the protocol was reported to the Clinical Trials data base [83]. Initially, two methodological studies were conducted to secure outcome validity and reliability before initiation of the RCT. Rationale and methodological considerations regarding each outcome are presented in section 8.1.4.

A fundamental property of a balanced 1:1 RCT design is the random allocation of participants to minimize allocation bias and to balance known and unknown factors in the assignment of treatment[84]. In the current RCT (*Study 3*) we applied a concealed randomization procedure. Allocation was conducted by the principal author after baseline assessment using sequences of opaque sealed envelopes. Concealment was secured by following procedure: A computer generated randomization sequence blocked in groups of four was produced and sequentially numbered closed envelopes containing allocation was produced. The sequence was produced by a person not otherwise affiliated with the study securing the concealment of the randomization sequence from the person enrolling patients.

Despite the RCT design the current study posses certain design limitations of which the risk of assessor bias and performance bias are the primary concerns.

Assessor bias may cause invalid conclusions regarding the intervention effect[85]. Generally, double blinded RCT designs are considered the gold standard for comparable study designs[86]. The primary

outcome in this study are the patient reported outcome 'ADL function' subscale of the Hip disability and Osteoarthritis Outcome Score (HOOS) which is self-reported by the participant. The data registration was performed blinded for allocation, thus the primary outcome was not subject to assessor bias. However, logistics at the combined test and training location made sufficient masking impossible and assessor blinding of the secondary outcomes regarding physical functioning and muscle function was not possible to implement. This poses a risk for assessor bias for these two outcome categories. However, the possible assessor bias was minimized by including only objective measurements collected following a highly standardized protocol for instructions and data collection.

Blinding of participants deals with the possible *performance bias* related to the participants awareness of being part of the active intervention group (or a part of an inactive control group) and can affect both self-reported and objective performance based outcomes. In the current study, performance bias may exaggerate between-group differences with the risk of introducing a type 1 error. In ideal double blinded designs, performance bias is managed by introducing a sham intervention for the control group, however given the present intervention with high intensity RT, it would be difficult to design a realistic and credible placebo exercise intervention without an additional exercise effect.

During the inclusion period the Danish health system provided a treatment guarantee of 1 month for hip OA patients scheduled for THA. Inconsistency in time to surgery between intervention group and control group was allowed to improve similarity between control group and the short waiting time in daily clinic. If the waiting period to surgery in the control group had been matched with the intervention group (an addition of 6 weeks), the prolonged inactive waiting period to surgery (compared to daily clinic) may have caused further deterioration of function and muscle outcomes in the control group (compared to daily clinic) eventually causing an exaggerated effect of the intervention (larger between group difference at follow-up) affecting the external validity of the results. The choice of study design may restrict the internal validity due to unmatched time to surgery between the two study groups. However, a recent meta-analysis provides strong evidence that self reported function and pain in hip OA patients do not deteriorate during waiting times (< 180 days) to THA [87].

Outcome reliability and agreement (regarding muscle function and physical functioning outcomes) was evaluated in a traditional test-retest study design (study 2) where a sample of patients with hip OA scheduled for THA was assessed at two separate standardised test occasions (see 8.1.3). To evaluate the validity of objective measured physical activity in hip OA patients (study 1), the outcome from a commercial available activity monitor was evaluated against a validated criterion method for

measuring energy expenditure (a portable indirect calorimetry monitor) during a protocol containing periods of rest and physical activity simulation activities of daily living (see 8.1.4).

8.1.2 Populations

Generally, factors related to the RCT design *per se* may restrict the generalization beyond the study population since introduction of inclusion and exclusion criteria can affect the external validity.

Inclusion criteria were kept wide (Table 1) and exclusion criteria were necessarily in order to define a representative study population for patients with hip OA scheduled for THA. In the RCT patients with an age of 50 years and above was included. Considering the CONTENT criteria proposed by Hoogeboom at al 2012[60] it can be argued that an even higher age limit may have increased the therapeutic validity of the intervention due to the reduced functional reserve capacity with increasing age[88]. Patients with severe walking deficits were excluded since a small pilot study indicated that these patients were not sufficiently supported by the group training design and would require individual training. This limits the interpretation of the study results regarding very frail hip OA patients and consequently, affects the external validity.

Table 1

Criteria of inclusion/exclusion for Study 2 and Study 3

Inclusion Criteria	Exclusion Criteria
• Diagnosed primary osteoarthritis of the hip and scheduled for surgery (THA) aged fifty years and older at the Department Orthopaedic, Herlev University Hospital	• Rheumatoid arthritis and other types of arthritis not diagnosed as OA • Uraemia • Cancer • Treatment with systemic glucocortioid > 3 months the last 5 years with a dose ≥ 5 mg • Present or previous hip fracture (both sides) • Other lower extremity fracture within one year prior to inclusion, body weight > 135 kg • Severe walking deficits (dependency of two crutches or walker for mobilization) • Inability to communicate in Danish language

*The RCT study population*Inclusion of eligible participants for the RCT took place from 1 of April 2011 to 1 of June 2012. Patients were diagnosed and scheduled for surgery by the hip surgeons at the Department of Orthopaedic Surgery, Herlev Hospital. All hip OA patients scheduled for THA were registered and primary hip OA patients scheduled for surgery were subsequently contacted by the investigator for eligibility (see CONSORT flowchart – Figure 3). Three hundred and thirty seven patients were assessed for eligibility of which 263 patients with an age of 50 years or older were scheduled for primary THA (Figure 3). Fifty three patients (20%) were excluded, leaving 210 patients eligible. One hundred and thirty of the eligible patients declined to participate in the RCT. The primary reason to decline participation was delay of surgery beyond the one month guarantee provided by the Danish Health Care System during the inclusion period (42%). As a consequence of the intervention, participation required the acceptance of delayed surgery for additionally 6 weeks (since patients allocated to the intervention group received 10 weeks preoperative intervention).

Theoretically, the postponed time to surgery applied to participants in the intervention group may have introduced a *selection bias* related to symptom state. However, a demographic analysis of the non-participants revealed no difference between the group of hip OA patients declining to participate in the study and the study population regarding age or gender distribution. However, since these patients were non-participants in the protocol, functional or pain characteristics were not available for analysis. Patients employed in day time jobs may also have found it difficult to participate in exercise sessions within normal working hours. However, only a minor number of patients reported problems attending their jobs as the major cause for declining participation.

Study populations specific for the methodological studies

For *Study 1(Paper I),* a convenience sample of 20 patients diagnosed with hip OA (10 of preoperative stage scheduled for THA, 10 of postoperative stage), were included (see Table 2) to validate physical activity measurements prior to application in the RCT. Recruitment took place from 1 June 2010 to 1 august 2010 at the Department of Orthopedic Surgery and Traumatology, Odense University Hospital. Twenty five were asked, 3 declined to participate and 2 were excluded (1 due to known symptomatic lung disease and 1 due to known symptoms of claustrophobia).

For *Study 2 (Paper II & III*), a convenience sample of 13 patients (Criteria; see Table 1) was recruited from the waiting list for THA at the Department of Orthopaedic Surgery, Herlev University Hospital, Denmark. Initially, fifteen patients were contacted consecutively of which 2 patients later declined to participate. Inclusion took place from December 2010 to January 2011.

Sample size

Sample size calculations directed intervention studies require an estimation of the variance in the study population and a definition of the size of change in primary outcome, representing a relevant clinical improvement.

According to the RCT we applied a sample size calculation based on the primary outcome the Hip dysfunction and Osteoarthritis Outcome Score (HOOS) subscale 'ADL function' (See 8.1.3*; Primary outcome*).

The clinical relevant change in HOOS ADL function subscale was *a priori* defined as a difference of 10 points as also used in on other studies[57]. Seventy-four patients were needed (SD 15, power: 0.8, α: 0.05). We subsequently included 40 patients in each group (80 patients in total) to encounter

loss to follow-up. With a loss to follow-up of 3 patients (intervention group (n= 2); control group (n= 1)), the calculated surplus proved to be adequate.

The population sizes used in *Study 1* and *Study 2* were based on general consensus in related literature and in accordance with an expert statistician.

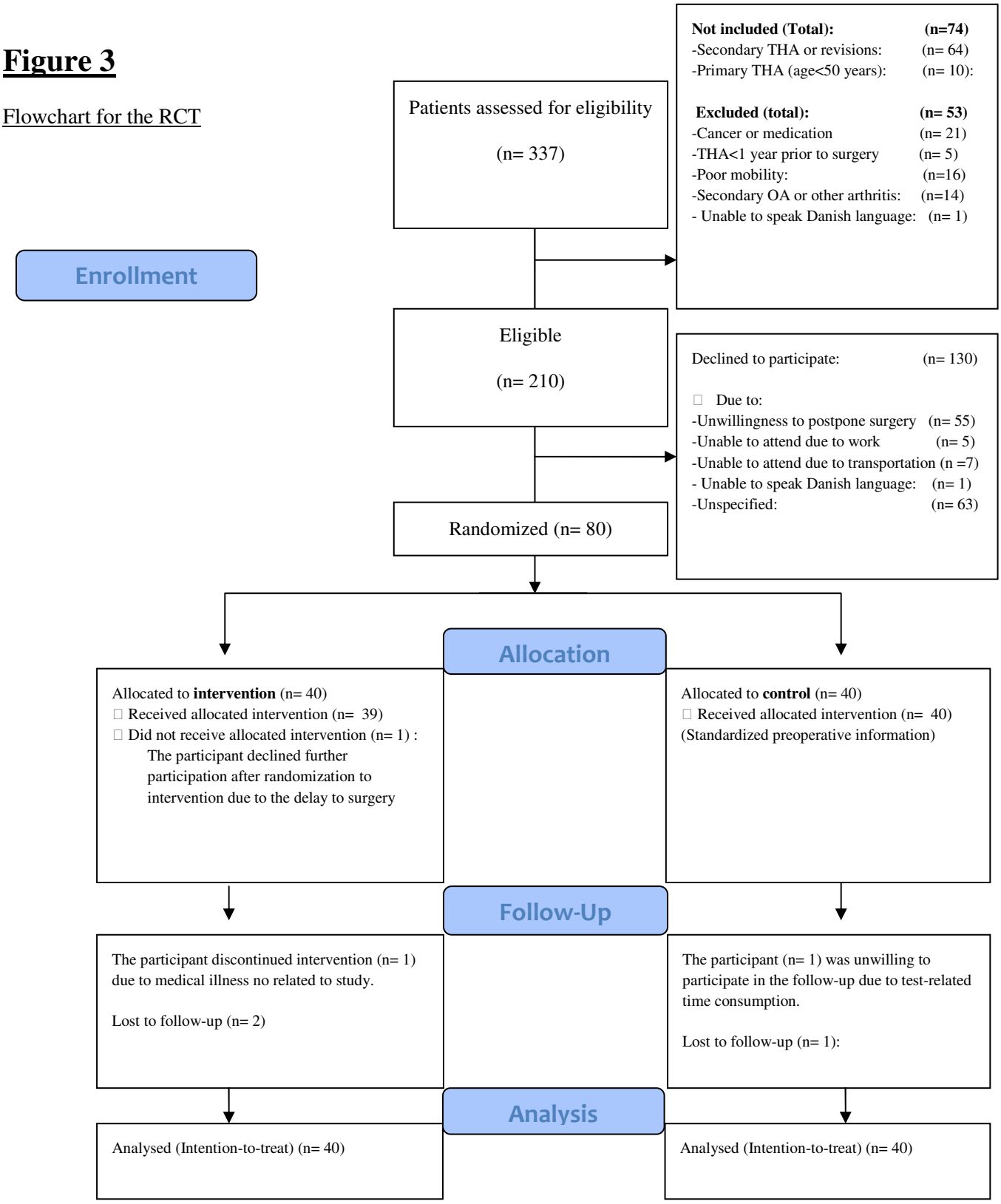
Table 2.

Criteria of inclusion/exclusion for study 1 (Paper I)

Inclusion Criteria	Exclusion Criteria
The preoperative group: • Diagnosed primary osteoarthritis of the hip and *scheduled for surgery (*THA) at the Department Orthopaedic Surgery and Traumatology, Odense University Hospital. **The postoperative group:** • Diagnosed primary osteoarthritis of the hip, *treated with THA* at the Department Orthopaedic Surgery and Traumatology, Odense University Hospital within 6 to 12 months of inclusion.	**Preoperative and postoperative group:** • Patients with a known history of symptomatic lung or heart disease • Known symptoms of claustrophobia or unease using a mask • Patients not understanding Danish language were excluded. • Patients dependent on a walking assistant device **The post surgery group:** • Patients scheduled for reoperation of THA or with a previous dislocation

Figure 3

Flowchart for the RCT



8.1.3 Outcomes

General considerations

The selection of outcome measures was carried out with the attention to physical function and disability found in hip OA patients scheduled for THA and involved health dimensions within the methodological framework of The International Classification of Functioning, Disability and Health core set for osteoarthritis [26].

According to the recommendations for RCT studies in general and intervention studies in OA in particular, a validated patient-reported outcome was selected as primary outcome for evaluation of the efficacy of the intervention [86,89].

Since the therapeutic rationale behind the intervention was to improve preoperative physical function through the enhancement of muscle function induced by explosive-type RT, we added a battery of functional performance measures and mechanical muscle function tests for explorative purpose. Physical performance measures have been recommended as an extension of patient-reported outcomes in hip OA to complement the description of the functional impairment in hip[90,91]. Body composition using dual-energy X-ray absorptiometry (DXA) was applied to quantify potential changes in fat free mass following intervention. In this context change in fat free mass was used as an approximation of change in muscle mass to substantiate potential training induced muscle hypertrophy. The outcome also constitutes an important addition to the outcome battery as the outcome (opposed to any self reported and performance based outcome) is not subject to performance bias.

Feasibility represents another important aspect of a clinical intervention. Providing a health care intervention, although potentially effective, is not necessarily well accepted by the study population, and this may affect the external validity of the findings [92]. In the present context of prolonged (10 weeks) high intensity RT in patients with symptomatic late stage hip OA, feasibility was investigated according to i) pain in relation to exercise, ii) adherence to training and iii) adverse events.

Pain and limitations in physical functioning associated with symptomatic hip OA may affect the general *physical activity* level towards a more sedentary lifestyle (see 6.3). Theoretically, improving physical functioning through conditioning of muscle function may increase the physical activity level with potential improvements in general health status. However, evaluation of physical activity in the hip OA patient poses a challenge, since objective measures of physical activity has not yet been validated within the patient group.

The patient reported outcomes

The Hip disability and Osteoarthritis Outcome Score (HOOS) [93] was chosen as patient reported outcome since it (compared to other questionnaires e.g the Oxford Hip score) offers a extended evaluation of daily functional impairment and pain.

The HOOS questionnaire is a validated hip OA specific patient reported questionnaire of 5 subscales reporting on 'ADL function', 'pain', 'other symptoms', 'sport & recreation function' and 'hip related quality of life' and includes the extensively used WOMAC (Western Ontario McMaster osteoarthritis score) Osteoarthritis Index LK 3.0[94]. The HOOS offers an extension of the WOMAC in form of the subscales 'sport & recreation function' and 'hip related quality of life' which addresses impairments in strenuous physical functions and the general satisfaction related to hip function.

The questions in each sub scale are answered by marking a 5 point Likert scale grading the problem being addressed from "None" to "Extreme" (rated 0 to 4 points) and the subscales have shown to be reproducible in hip OA patients (ICC >0.78) [95]. A normalized score (0 to 100) is calculated for each subscale separately with 0 indicating worst symptoms and 100 indicating no symptoms. The questionnaire address pain or functional impairments experienced during the last week and to avoid any bias from pain related to the physical tests contained in the current protocol, the questionnaire was provided prior to any physical activity related to tests.

Primary Outcome

The subscale 'ADL function' was selected as primary outcome since the intervention with explosive-type RT was targeted improvements in physical impairment through enhancement of leg muscle function. The 'ADL function' subscale contains 17 questions related to physical functioning in daily living. The remaining subscales 'pain', 'symptoms', 'sports & recreation' and 'hip related quality of life' were reported as secondary outcomes.

Despite being recommended as primary outcome, patient reported outcomes have several limitations. As the outcome is self reported it will be dependent on the individual context of the participant regarding his/her physical capacity, need and expectation related to functional tasks. The use of a limited scale (like the 5 point Likert scale in HOOS) introduces the risk of floor and ceiling effects for individuals who score near the extreme values of the scale. The construct validity of the outcome is important as it describes how well the questionnaire measures the construct of interest (in this case

function and pain in hip OA patients). Another challenge is the ability to detect changes (responsiveness) and to define (and detect) clinical changes of relevance. The HOOS has been tested for both construct validity and responsiveness [93,96] .

A 10 points change on the ADL function subscale have been suggested clinical relevant and applied in previous research[57] as well as in the current study. Essentially, this cut-point of 10 point is an *a priori* definition since the clinical relevant difference for HOOS outcomes in late stage hip OA patients prior to THA remain to be described. A change of 7.9 on the WOMAC 'function' (identical to HOOS ADL function) has previously been suggested a 'minimal clinical important improvement' for hip OA patients in medical treatment with NSAID[97]. Meanwhile, since Tubach et al. did not include patients scheduled for surgery, the possible discrepancy in the symptom state between the study populations may affect the interpretation in relation the current study. A different approach based on the definition of a set of responder criteria have been proposed using both the relative and absolute individual changes in symptom state, however their application requires addition of a global assessment tool which was not included in the current study design[98]. Recently, minimal clinical important improvements regarding HOOS outcomes have been investigated following hip replacement surgery suggesting a change of 23 HOOS points on the ADL function sub scale[99]. Importantly, this study evaluated minimal clinical important improvements related to major surgery (THA), which restricts the comparability with a non-surgical intervention with a different risk profile.

Muscle function outcomes

Leg muscle function was evaluated in terms of maximal leg extension muscle power (defined as the force exerted timed the velocity during a bi-articular leg extension movement) and single-joint peak isometric muscle force and rate of force development (explosive muscle characteristic during isometric contraction) for hip and knee extension (for detailed descriptions; see Paper 2 and 3). Explosive force is considered an important functional isometric outcome since the ability to rapidly increase force during the initial phase of muscle contractions is believed to be more important than maximal peak force in many aspects of ADL including reversing from a fall[54,55,77].

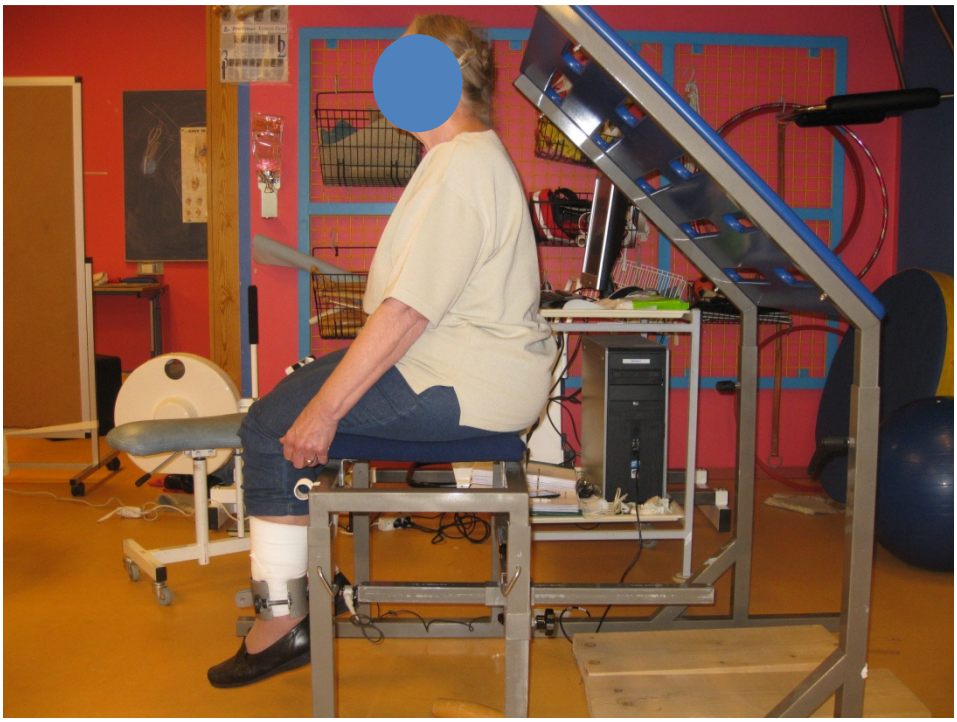
Leg extension muscle power was measured during leg press performed seated in the Nottingham Power rig (Figure 4) [34,37]and is associated with important motor tasks like gait speed, stair climb and repeated chair rise in frail elderly [34,37,100]. To explore possible discrepancies in training effect between muscle groups and the relation to functional outcomes, single-joint isometric muscle tests during isolated knee and hip extension (Figure 5) were applied.

Figure 4

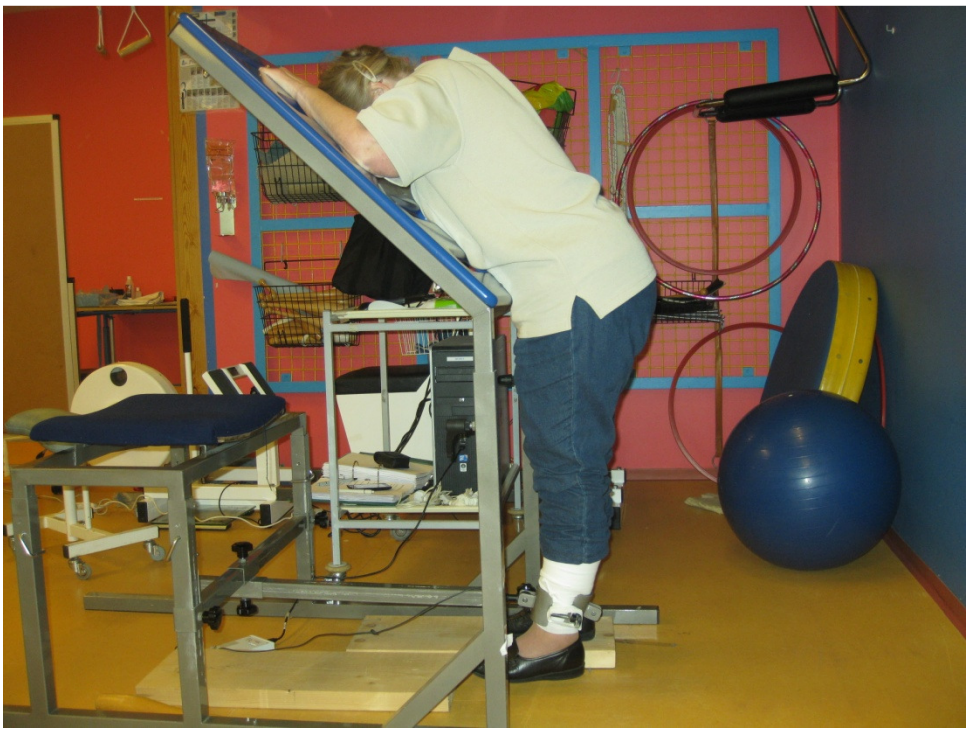
Leg extension power measured seated in the Nottinham Power Rig

Figure 5

The custom made test chair for isometric knee extension measurement using strain gauge technique. The clamp is positioned just above the ankle and connected to a dynamometer fixed on the metal lever.



Isometric hip extension was measured in standing position with 45 degrees forward inclination.



Physical performance measures

The functional performance measures (i.e. horizontal gait (normal and maximal speed), stair climb (ascending and descending) and chair rise (sit-to-stand)) were selected to reflect the impairment of

physical functioning important for common ADL tasks[25,101]. Stair negotiation and fast horizontal walking were included since the decline in functional capacity with increasing age may pose a particular threat to independence in strenuous activities[76,88]. At the time when the present protocol was designed, no consensus regarding functional performance tests in prospective studies of hip OA patients existed. Recently, a OARSI recommendation has been published[91] including a fast walk tests, stair climb and chair stand among 5 recommended physical function tests to complement patient reported outcomes in prospective studies.

Reliability of Functional Performance Measures and Muscle Function Tests

The battery of functional performance measures and measurements of leg muscle power and isometric muscle strength was tested for reproducibility in terms of agreement and reliability. Results of the reliability study are reported in Paper 1 and Paper 2.

Reliability (interclass correlation coefficient (ICC)) constitutes an important aspect of the precision of a quantitative outcome measure because it describes the variability of measurement error compared to the variation between subjects (or how well a given outcome measure is able to discriminate between individuals). Test-retest agreement (coefficients of variance (CV) describes how closely repeated measurements are distributed within a certain time frame in a particular population tested under otherwise identical circumstances. Acceptable test-retest agreement is important for repeated measurements used in a prospective study design.

Intra-examiner reliability of functional performance (stair climb, horizontal walking and 5 times sit-to-stand) and muscle function (leg extension power and isometric strength) was tested in a test-retest study on two occasions separated by 7-10 days, using the identical test facility and equipment later to be used in the RCT. The procedure for measurements and testing conditions were strictly standardized. Prior to testing the participants underwent 5 minutes of warm-up on a stationary exercise bike with low resistance. Muscle function outcomes were tested on each leg separately followed by the functional performance tests.

The outcomes included in the test battery regarding physical functioning tests and leg muscle strength/power all had acceptable reliability and agreement sufficient for between-group analysis (See section 8.2.1) and therefore applied in the following RCT. Regarding the muscle function test, results were in accordance with previous findings in healthy elderly [102] and patients with hip/knee OA [103].

Body composition

The principle of analyzing body composition using dual-energy X-ray absorptiometry (DXA) is to divide total body mass into three tissue compartments; bone mass, fat mass and fat free mass at a molecular level[104] . In the current study we used a full body mini fan beam DXA (Lunar Prodigy scanner (GE Lunar, Madison WI, USA)) to measure changes in body composition with the particular interest in fat free mass as an approximation of changes in muscle mass. Excellent test–retest agreement (CV; 0.92%) has been established for the specific scanner used in the present study regarding measurement of fat free mass (unpublished data).

The technique is based on the attenuation of X-ray beams with dual photon energy and uses differences in the mean density of tissues and subsequently the attenuation of X-rays to discriminate between the three tissue components; bone, fat and fat free mass[104]. Each atomic element have a characteristic mass attenuation coefficient for a given photon energy. When photons at two different energies pass through a tissue, attenuation can be expressed as a ratio of attenuation. Since the attenuation ratio is known for different body tissues (e.g. bone mineral, water, protein, fat) the measured ratio reflects the tissue mass[105]. First the amount of bone is determined and then by further analysis of the soft tissue to measure the amount of fat and fat free mass, estimated to have a mean density of 0.9 and 1.1 g/cm3, respectively.

DXA has been validated against computer tomography (CT) and magnetic resonance (MR) (both regarded criterion methods in elderly) and DXA fat free mass is reported reliable and valid as an estimate for muscle mass[106–108]. For analysis of regional changes in fat free mass, the femoral region was selected as the area of interest according to the muscle groups targeted by the intervention and femoral fat free mass was estimated using validated regional landmarks [107,108]. The advantages of the method include observer independence and no risk of performance bias which is particular important as a complement to the battery of performance based and self-reported outcomes used in the current study. For repeated measurements (as applied in the current RCT) the method is superior to CT with regard to low exposure risks for the participants and total costs. However, the DXA method posses limitations which have implications related to the current study; the method does not discriminate between muscle groups and the method may be inferior to CT for detection of quantitative muscle changes[109]. Furthermore, the validity is reduced in very lean or highly obese subjects and variation is observed between different scanners[104]. The latter limitation was avoided in the present study by using a single scanner for all measurements.

8.1.4 Validation of physical activity in patients with hip OA (*Paper I*)

For the investigation of free living physical activity (see section 6.3) in a RCT, small body-worn multisensory activity monitors may constitute a valid and objective surrogate outcome[49,110–115]. However, the studies of patients with hip OA are still few and their results are restricted by the general lack of validation in patients with degenerative joint disease[49,116,117].

Before the application of activity monitor based estimates of physical activity as an outcome in a RCT it was warranted to investigate the validity in patients with hip OA according to; i) bias between activity monitor estimates and criterion method, ii) correlation between methods and iii) difference in variance [118]. We used a portable system for indirect calorimetry (Figure 6) for validation of physical activity in terms of energy expenditure which is a preferred criterion method during short term free living validation protocols containing both indoor and outdoor activities[119–121].

Figure 6

The multisensory activity monitor Sensewear Pro3 armband. The activity monitor is positioned at the midpoint of the right upper arm. The monitor requires only positioning as it activates automatically by skin contact (for more details – see text)

The K4B metabolic monitor for measurement of indirect calorimetry. The apparatus weights 1.5 kg and includes the metabolic monitor, a battery pack and mask worn throughout the experiment.

We evaluated the validity during a 2 hour protocol of various activities simulating common ADL ranging from supine rest till fast walking/jogging, in which the energy expenditure in 20 hip OA patients (10 preoperative and 10 postoperative) were recorded simultaneous by indirect calorimetry (criterion method) and the activity monitor (Figure 6).

The findings (see section 8.2.2) oppose previous findings in healthy adults where the current activity monitor has been reported reliable [114,115] and valid for estimation of cumulated daily energy expenditure [111,122]. However, limitations in validity have been reported in specific activity types [123–126], in healthy older adults [110,127], obese adults [114] and in various patient groups, including patients with rheumatoid arthritis[112,128–130].

The present findings indicate that the activity monitor is subject to pronounced bias in hip OA patients during common ADL which represents a major concern for the validity in this patient group. The study has limitations regarding generalization due to the sample size and restricted number of activities included in the protocol. In addition the study population was slightly younger and with a surplus of male patients compared to the later RCT (Table 4).

Opposed to the hypothesis, it was concluded that the current findings of low validity in common ADL excluded the application of the activity monitor in the RCT. Further development regarding the method and its validity is warranted before it can be considered a valid outcome measure for patients with hip OA.

8.1.5 Intervention with explosive-type RT

The disability and joint dysfunction present in symptomatic OA is believed to contribute to the impaired muscle strength and muscle atrophy observed in hip OA[41,131,132] and impaired leg muscle strength has been identified as a predictor for poor functional outcome after THA[30]. Despite functional improvements after surgery, a prolonged loss of muscle strength with potential relevance for activities of daily living is reported after total hip arthroplasty (THA) [25,41,43].

The leg extensor muscles in particular play an important role in physical demanding ADL functions [34] and impaired leg muscle strength prior to surgery may affect ADL functions throughout the rehabilitation period after THA[30]. As a consequence the age related decay of functional reserve capacity observed in healthy elderly[76,88] may become accelerated in elderly individuals with hip OA and by time impose a threat to functional independence[101]. The therapeutic rationale behind the intervention program was to enhance preoperative physical function through specific conditioning of leg muscle strength/power by explosive-type RT of the lower extremities. The primary targets were the knee and hip extensor and flexor groups since deterioration of these muscle groups is most consistently reported in hip OA[38] and predicts poor functional outcome after THA[30].

No consensus exists regarding the adequate intervention period of RT to improve physical function in elderly; however interventions between10 and 12 weeks are commonly applied[76,77,133]. For the current intervention a 10 week training program of preoperative explosive-type RT was applied with two weekly sessions supervised by trained physiotherapists. The dose and intensity followed

the guidelines for progressive RT in healthy elderly by the American College of Sports Medicine[73,134].

The exercise program consisted of 4 stations and 3 series within 8-12 repetitions maximum were performed for each exercise. The concentric phase was performed as explosive as possible and the concentric phase was performed more slowly emphasizing a controlled motion. Resistance was adjusted according to the repetitions maximum at each session to promote progression. A detailed description of the exercise program (Figure 7) is provided in Paper 2 and 3.

For elderly hip OA patients presumable unfamiliar to the principles of progressive RT it was important to secure proper intensity level and progression during exercises. Therefore the training groups were kept small (with a maximum of 8 participants supervised by 2 physiotherapists) and individual progression for each participant was closely supervised and recorded. To improve adherence, the exercises were conducted pair-wise with the same training partner ('buddy training') throughout the intervention period.

The Control Group

The control group received 'care as usual', which besides the standardized pre-operative information by the hip surgeon, included a 4 hour information meeting at the Department of Orthopedic Surgery held by nurses and physiotherapists and a handout suggesting low-intensity home-based training program without specific RT exercises. To improve external validity there were no restrictions in engaging exercise programs outside the study.

Figure 7

Explosive-type RT during leg press. Range of motion is commonly impaired in patients with hip osteoarthritis. Hip inclination was adjusted individually to secure maximal range of motion during the leg press exercise.

Explosive-type RT during knee extension. The participants were teamed up with the same training partner throughout the intervention period. The partner kept record of repetitions and loading and cheered during the sets.

8.1.6 Feasibility

In relation to the present intervention with explosive RT in patients with symptomatic hip OA scheduled for THA, feasibility may address areas like; i) aspects of the intervention which may restrict the compliance in the study population (e.g. high levels of experienced pain in relation to exercise) ii) acceptance of the intervention (drop-outs and adherence to the program) and iii) adverse events (defined as medical illness, musculoskeletal injury or cancelled sessions due to pain and/or injuries) [135].

To investigate the extend of exercise related pain was monitored [57,135,136]. The musculoskeletal pain before and immediately after exercise and the delayed onset of muscle soreness the following day were assessed using a continuous visual analog scale (VAS) with 0 being no pain and 10 worst imaginable pain. Pre-defined cut-off points that have previously been applied in physical intervention in a similar patient group were used for "acceptable" pain were used; 'safe'; VAS≤2, acceptable; 2<VAS≤5 and 'high risk'; VAS>5[135].

Participants were informed that delayed onset of muscle soreness after RT was expected especially for participants previously unfamiliar with RT. However, pain the day after training should not exceed the individual 'normal' pain level for the participant. If scores were exceeding these limits the training intensity was diminished the following session. Dropouts, adverse events and adherence (attended sessions) were registered. Good compliance was *a priori* defined as an attendance to training of 80% (corresponding to 8 weeks of full training).

8.1.7 Statistical analysis

Study 1

The analysis of the validity was based on three proprieties: i) Bias (difference) between activity monitor estimates and criterion method, ii) correlation between the two methods and iii) difference in variance [118].

The statistical analysis was performed using functional data analysis[137] which, opposed to a more constrained approach based on linear mixed models, offer full flexibility over the time scale with minimal assumptions. For the comparison of the two methods the functional mean was estimated leading to the definition of a time dependent bias function (describing the difference between the methods). Secondarily, the functional variance processes [138] and the correlation coefficient was estimated [139]. Since a two-way functional ANOVA model showed no significant effect of being in the pre or post surgical group, this factor was removed and pooled data was used in the analysis.

Statistical analysis was carried out using R version 2.15.2 (2012-10-26)"Trick or Treat" Copyright (C) 2012 The R Foundation for Statistical Computing ISBN 3-900051-07-0

Study 2

The within-subject coefficient of variation $CV_{within\text{-}subjects}$ was calculated as the percentage of the standard deviation to the grand mean difference (between test and retest) and used as a measure of agreement to describe the standard error of the measurement (including both biological variation and measurement error)[102]:

$$CV_{within\text{-}subjects} = \frac{SD}{\overline{X}} \times 100$$

Where $SD = \sqrt{\frac{\Sigma(d^2)}{2n}}$, where d= test – retest and n = number of participants

$$\overline{X} = \frac{\overline{X}\,test - \overline{X}\,retest}{2}$$

Analysis was carried out with a conservative approach to outliers with no data points omitted.

Reliability was calculated using the intraclass correlation coefficient (ICC) which can be interpreted as the proportion of the total residual variance that is due to the residual variability between subjects:

$$\frac{\sigma_\alpha^2}{\sigma_\alpha^2 + \sigma_\epsilon^2}.$$

The calculation of ICC was based on large one-way analysis of variance carried out using STATA 11.1, StataCorp, Texas, USA.

Study 3

Following the CONSORT statement recommendations, the outcomes at baseline and follow-up are reported in mean (±1SD) and the contrasts between groups are reported as adjusted between-group differences at follow-up with 95% confidence intervals. Adjusted between group differences mean (95%CI) at follow-up was analyzed by a multilevel regression model adjusting for baseline, group, gender, age and BMI. A two-sided p-value of 0.05 was set as significance level providing evidence against the null hypothesis.

Intended-to-treat analysis was selected as the primary analysis to avoid any bias associated with potential non-random loss to follow-up. All patients randomly assigned were included for the analysis and baseline observation was carried forward in cases where data were missing. However, there was no difference between intention-to-treat and per-protocol analysis.

Associations between changes in muscle function and changes in physical ADL functions and body composition (fat free mass) were analyzed to identify muscle determinants relevant for improvements in ADL function. Analysis for associations between changes in muscle strength characteristics, functional outcomes and body composition were carried out using simple regression.

Describing group differences exclusively by p-value describes the probability that a difference of at least the same size would have arisen by chance, however; it does not quantify the size of difference between groups. Instead, *effect size* is a way of quantifying the size of the difference between two groups using the standardized mean difference (SMD). Effect size was reported using Cohen's *d* with indexes for small, medium and large effect as proposed by Cohen, 1992[140].

Software used for statistical analysis of study 3: STATA 11.1, StataCorp, Texas, USA.

8.2 Results

Methodological studies:

8.2.1 Reliability and agreement of muscle function and physical performance tests (*Paper II & III*)

Good to moderate agreement ($CV_{within\text{-}subjects}$, range = 4.2%-13.9%) and good to excellent reliability (ICC = 0.82 – 0.97) was observed in all functional performance outcomes.

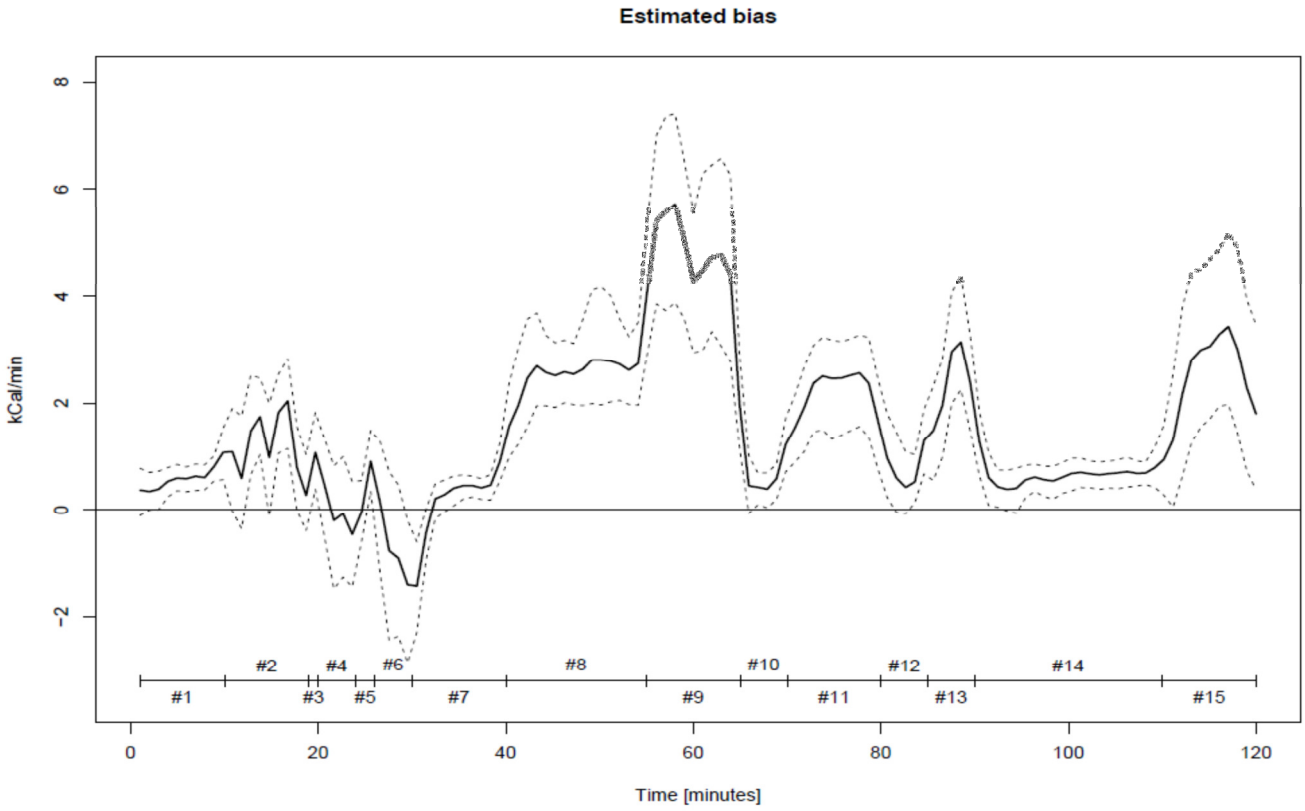
Isometric knee extension showed moderate agreement ($CV_{within\text{-}subjects}$ = 11.5% and 16.7% for affected and non-affected leg, respectively) and good reliability (ICC =0.90 and ICC = 0.70 for affected and non-affected leg, respectively). For isometric hip extension moderate agreement ($CV_{within\text{-}subjects}$ = 9.5% and 15.6% affected and non-affected leg, respectively) and good to excellent reliability (ICC = 0.96 and ICC = 0.87 affected and non-affected leg, respectively) was observed.

Good agreement ($CV_{within\text{-}subjects}$ = 6.3%) and excellent reliability (ICC = 0.97) was observed for leg extension power on unaffected leg whilst moderate agreement ($CV_{within\text{-}subjects}$ = 15.7%) and good reliability (ICC=0.84) was observed on the affected leg.

Figure 8

Bias between Sense Wear Pro3 (SWA) estimates and indirect calorimetry.

Bias expressed as the mean difference with 95% confidence intervals. Zero on the Y axis represents no difference between the methods. A positive value represents an overestimation of SWA. Coding #1-#15 represents intervals of steady state activity (see Table 3).



8.2.2 Validity of objective measured physical activity in hip OA patients *(Paper I)*

The correlation coefficient between the criterion method and the activity monitor (all activities) was 0.94. However, significant bias (over or underestimation) was reported during most activities (Fig 8). On average the energy expenditure by the activity monitor during all activities was 72% overestimated. During horizontal walking (all speeds) an overestimation between 62% and 93% was recorded while energy expenditure was underestimated during stair negotiation (-25%). Intervals dominated by upper body movement showed large overestimation with 170% and 119% recorded for outdoor gardening and indoor cleaning, respectively (Table 3). When analyzing variance processes of the activity monitor estimates vs. indirect calorimetry the activity monitor was less stable in most activities apart from periods of rest.

Table 3

The activity types of the protocol with coding for intervals. Mean values of energy expenditure (EE) measured by Sense Wear Pro3 (SWA) and indirect calorimetry (IC) and absolute and relative bias between units[1]. Positive bias values indicate overestimation of SWA.

Activity Type	Length (min)	Interval	EE SWA (Kcal/min)	EE IC (Kcal/min)	Bias (Kcal/min)	Bias (%)
Total	**120**		**3.7 [3.4;4.0]**	**2.2 [1.8;2.6]**	**1.54 [1.3;1.8]**	**71.8 [51.7;92.8]**
Resting in chair	10	#1	1.5 [1.4;1.6]	0.9 [0.7;1.1]	0.6 [0.5;0.8]	77.8 [45.2;117.5]
Work out (steps and multi planar movements)	9	#2	4.2 [3.8;4.6]	3.0 [2.5;3.5]	1.2 [0.7;1.6]	40.3 [21.0;60.8]
Resting in chair[2]	1	#3	3.0 [2.6;3.4]	2.3 [1.9;2.7]	0.7 [0.1;1.2]	29.6 [5.4;57.3]
Sitting/standing and walking between 2 chairs	4	#4	3.6 [3.1;4.1]	3.8 [3.2;4.4]	-0.2 [-0.8;0.4]	-4.7 [-19.6;10.5]
Resting I chair[2]	2	#5	2.6 [2.0.25;3]	2.1 [1.6;2.5]	0.5 [0.1;1.0]	27.0 [2.4;59.3]
Stair climbing (5 steps up/down)	4	#6	3.1 [2.7;3.6]	4.2 [3.6;4.9]	-1.1 [-1.8;-0.3]	-24.8 [-39.1;-7.6]
Resting in a supine position	10	#7	1.5 [1.3;1.6]	1.0 [0.8;1.2]	0.5 [0.3;0.7]	53.1 [25.6;81.0]
Walking normal speed (self paced)	15	#8	5.8 [5.1;6.5]	3.0 [2.5;3.5]	2.8 [2.3;3.3]	93.3 [72.0;119.1]
Outdoor gardening (raking leaves)	10	#9	7.0 [6.1;7.8]	2.6 [2.2;3.1]	4.4 [3.8;5.1]	170.3 [134.0;211.4]
Resting in chair	5	#10	1.8 [1.6;2.0]	1.0 [0.8;1.3]	0.8 [0.5;0.9]	73.9 [42.5;105.7]
Brisk walking	10	#11	5.7 [5.2;6.2]	3.5 [2.9;4.1]	2.2 [1.7;2.6]	62.9 [42.3;87.2]
Resting in chair	5	#12	2.1 [1.8;2.4]	1.2 [1.0;1.5]	0.9 [0.6;1.2]	71.8 [41.3;107.7]
Jogging/brisk walking	5	#13	6.1 [5.2;7.2]	3.8 [3.1;4.5]	2.3 [1.8;2.9]	61.9 [45.3;81.9]
Resting in chair	20	#14	1.4 [1.3;1.5]	0.8 [0.6;1.0]	0.7 [0.5;0.8]	88.0 [47.2;136.2]
Sweeping floor	10	#15	5.0 [4.2;5.8]	2.3 [1.9;2.8]	2.7 [1.9;3.5]	119.4 [75.0;172.1]

[1] Values are $\bar{x}$ with 95% confidence interval. [2]Regarded as non-conclusive due do short time period

The RCT:

8.2.3 Preoperative explosive-type RT in hip OA patients scheduled for THA (*Paper II & III*)

The study population; flowchart of participants

The 80 patients eventually being randomized for the RCT were on average 70.4 ± 7.6 years at baseline and 65% (n=52) were female (Table 4). No difference in age and gender of the 130 eligible patients unwilling to participate were observed (Table 4). Three patients were lost to follow-up of which two patients were allocated to intervention: One patient (female) withdrew from the intervention group between baseline measurements and first exercise session due to the postponed time to surgery and one patient (female) did not complete intervention (and planned surgery) due to illness not related to intervention (pneumonia). In the control group one patient (male) withdrew due to the time consumption related to testing (Figure 3).

Outcome measurements regarding preoperative efficacy were collected at two occasions; baseline (prior to randomization) and follow-up (1-3 days before surgery). Outcomes regarding feasibility were registered at each training session for participants in the intervention group.
Mean time between baseline and follow-up was 10.5 weeks for the intervention group and 3.5 weeks for the control group.

Feasibility of preoperative explosive-type RT (Paper II)

For the 38 patients completing the exercise the average adherence to training sessions was 93 % and they all completed with an individual attendance ≥ 80% which was in accordance to the *a priori* definition of good compliance. VAS ≤5 immediately after training was reported in 95% of the sessions, whileVAS≤5 within training and/or the following day was reported in 83% of the sessions. Acute exercise related musculoskeletal pain (VAS>5 immediately after training) was reported in 9% of the early sessions (week 1+2) and 1% of later sessions (week 9+10). VAS>5 one day after training was reported in 34% of the early sessions (week 1+2) and 6% of the later sessions (week 9+10). Only two exercise sessions was skipped due to pain (one patient). No patients withdrew from IG due to pain or musculoskeletal injury. One patient reported temporary swelling and pain of the knee joint.

Table 4

Subject baseline characteristics for the RCT study (Paper 2&3). Data are $\bar{x}$±SD.

	All patients (n=80)	Control (n=40)	Intervention (n=40)
Female gender (N)	52	25	27
Age (years)	70.4 ± 7.6	70.8 ± 7.5	70.0 ± 7.7
Weight (kg)	77.4 ± 15.0	76.5 ± 13.5	78.3 ± 16.5
Height (m)	167 ± 9	167 ± 10	167 ± 9
BMI (kg/m^2)	27.8 ± 4.6	27.4 ± 3.8	28.2 ± 5.3

Subject baseline characteristics for the validation study (Paper 1). Data are $\bar{x}$±SD.

	All patients (n=20)
Female gender (N)	8
Age (years)	63.3 ± 9.2
Weight (kg)	82.8 ± 15.0
Height (m)	174.2 ± 7.7
BMI (kg/m^2)	23.7 ± 3.8

Subject baseline characteristics for the Reliability study (Paper 2&3). Data are $\bar{x}$±SD.

	All patients (n=13)
Female gender (N)	7
Age (years)	69.1 ± 8.6
Weight (kg)	75.4 ± 10.0
Height (m)	171.1 ± 8.2
BMI (kg/m^2)	26.9 ± 3.9

Efficacy of preoperative explosive-type RT on self-reported outcomes (Paper II)

Primary outcome: A 9.7 points 95%CI [4.3; 15.2] in-between group difference HOOS ADL in favour of the intervention group was observed at follow-up (p=0.001) (table 5) corresponding to an effect size of 0.8.

Secondary outcomes: All remaining HOOS sub scales ('Pain', 'Symptoms', Sports and Recreational Function, Hip Related Quality of Life') showed significant difference between groups at follow-up in favour of IG (p-value< 0.03) (table 5) with effect sizes between 0.4 and 0.6.

Table 5

The effects of explosive-type resistance training on patient reported outcomes. Outcomes at baseline and follow-up are $\bar{x}$±SD. Adjusted between-group differences are $\bar{x}$(95% CI). Between-group difference at follow-up is adjusted for baseline, sex, age and BMI. Cohen's *d* is calculated using pooled SD.

	Intervention Group		**Control Group**			
Outcomes	Baseline	Follow-up	Baseline	Follow-up	Adjusted between-group difference at follow-up*	Effect size Cohen's *d* (95%CI)
Primary Outcome HOOS						
ADL function	49.2(12.5)	58.9(17.3)	48.1(13.8)	48.3(13.9)	9.7(4.3 to 15.2)	0.8(0.3 to 1.2)
Secondary Outcomes HOOS						
Pain	48.0(12.7)	55.4(16.9)	46.3(14.4)	45.9(14.1)	8.2(2.1 to 14.3)	0.6(0.2 to 1.1)
Symptoms	44.5(16.4)	55.9(19.6)	43.1(18.5)	45.3(16.7)	10.3(4.0 to 16.5)	0.6(0.2 to 1.1)
Sports & Recreation	28.1(15.2)	37.8(18.7)	27.8(17.7)	28.3(15.4)	9.9(3.4 to 16.4)	0.6(0.2 to 1.1)
Hip related QOL	32.1(14.4)	38.6(17.1)	29.2(15.6)	30.5(14.3)	6.2(0.5 to 11.8)	0.4(0.0 to 0.9)

Preoperative explosive-type RT and the effects on muscle function, physical performance and fat free mass (Paper II & III)

Leg extension power: For both the affected and unaffected leg the leg extension power was significantly higher in the intervention group compared to controls ($p<0.0001$) with a similar between group difference at follow-up for both legs (Table 6). Maximal isometric strength: Significant between-group differences ($p<0.0001$) were observed for knee extension and hip extension (both sides) at follow-up (Table 6). Rate of force development: Significant between group differences at follow-up were observed in knee extension (both sides), $p<0.047$ and hip extension (affected side), $p= 0.02$ (Table 6).

Functional performance tests: For all functional tests the intervention group performed significantly better than controls at follow-up ($p<0.0001$) with following between-group differences: Stair climb speed 0.4 steps/second 95% CI [0.2; 0.5]; normal and maximum gait speed (20 meters) 0.1

meters/second 95% CI [0.1; 0.1] and 0.2 meters/second 95% CI[0.2; 0.3], respectively; 5 times sit-stand -2.2 seconds 95% CI[-3.2; -1.1](Table 6).

Body composition: Total lean body mass was 0.67 Kg 95% CI [0.1; 1.1] larger in intervention group compared to controls ($p = 0.013$) at follow-up (Table 6) with an effect size of 0.1. No significant changes were seen in fat mass or BMI between groups. According to regional (femoral) FFM, significant between group differences ($p<0.001$) were observed for both sides at follow-up (Table 6).

Correlation analysis: Significant associations with moderate linear relationship in the intervention group between pre to post training changes in stair walk speed and changes in knee extension MVC (affected side) were observed ($r = 0.34$; $p= 0.029$ and $r = 0.39$; $p= 0.012$, for ascending and descending stairs, respectively) (Figure 9). Similarly, change in descending stair walk speed was associated with changes in knee extension RFD ($r = 0.41$; $p = 0.009$ and $r=0.30$; $p=0.005$ for affected and unaffected side, respectively). However, no significant associations were found between changes in horizontal speed (self selected and maximal) or 5 times sit-to stand and changes in MVC or RFD (hip or knee).

Table 6

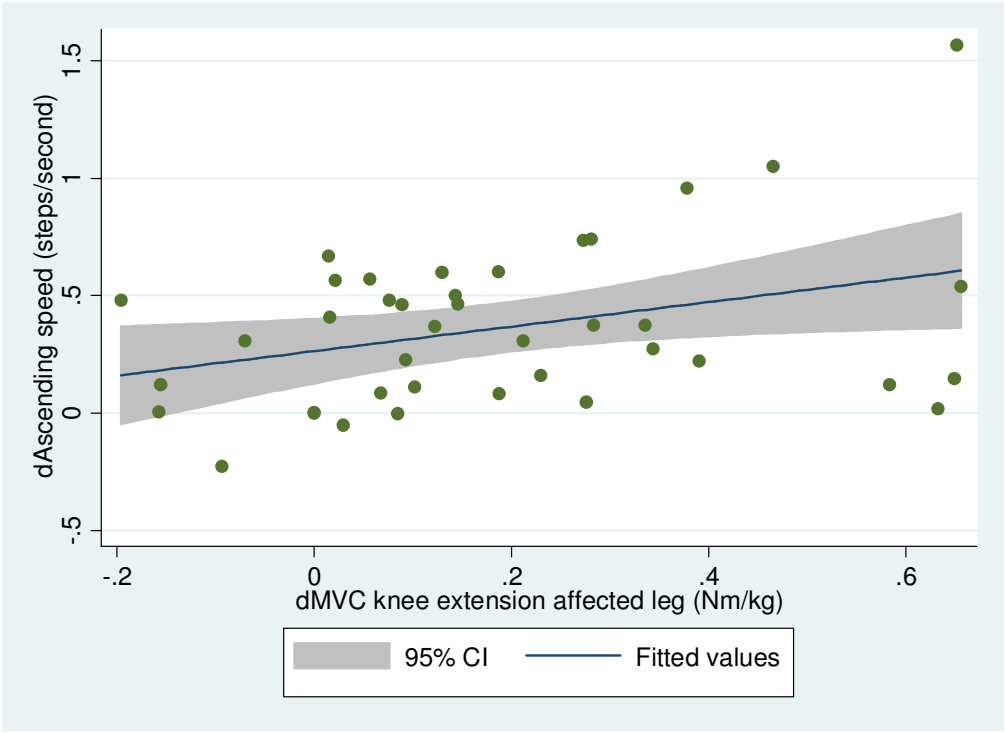
The effects of explosive-type resistance training on single joint isometric muscle strength, leg extension power, functional performance tests and fat free mass. Outcomes at baseline and follow-up are $\bar{x}$±SD. Adjusted between-group differences are $\bar{x}$(95% CI). Cohen's *d* is calculated using pooled SD.

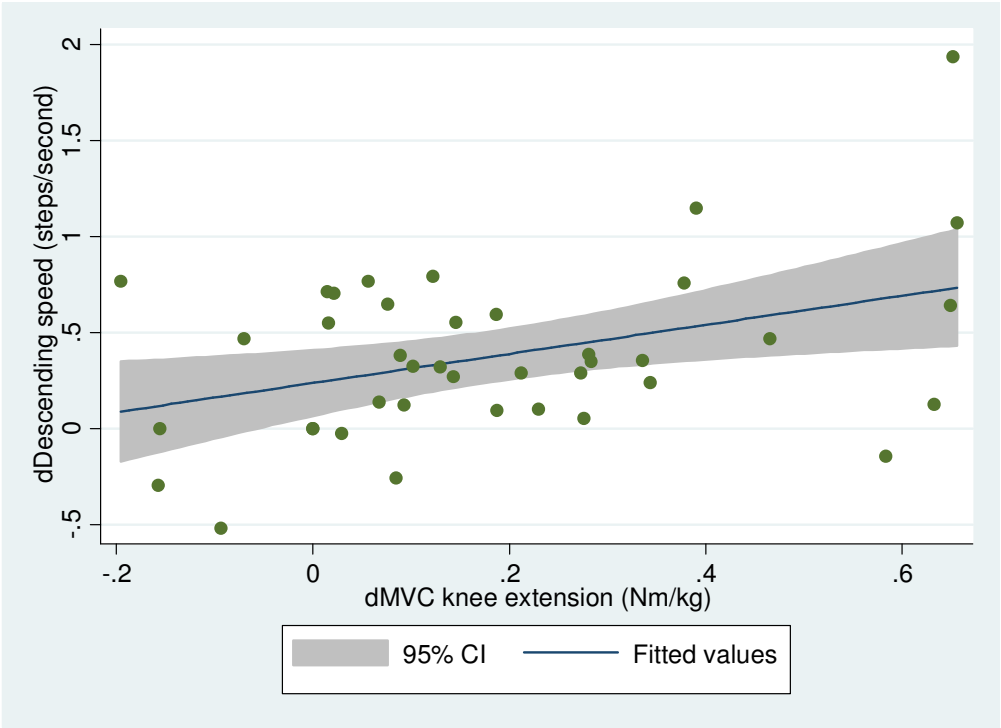
	Intervention Group		**Control Group**			
Outcomes	Baseline	Follow-up	Baseline	Follow-up	Adjusted between-group difference at follow-up*	Effect size Cohen's *d* (95%CI)
Leg muscle strength						
MVC Knee extension affected side (Nm/Kg)	1.17(0.39)	1.36(0.39)	1.17(0.45)	1.10(0.43)	0.27(0.18 to 0.35)	0.6 (0.2 to 1.1)
MVC Knee extension Unaffected side (Nm/kg)	1.30(0.44)	1.50(0.51)	1.29(0.46)	1.20(0.41)	0.31(0.22 to 0.40)	0.6 (0.2 to 1.1)
MVC Hip extension Affected side (Nm/Kg)	1.52(0.58)	1.85(0.60)	1.57(0.64)	1.53(0.60)	0.40(0.24 to 0.49)	0.5 (0.1 to 1.0)
MVC Hip extension Unaffected side (Nm/kg)	1.61(0.55)	1.97(0.62)	1.62(0.67)	1.61(0.60)	0.40(0.30 to 0.51)	0.6 (0.1 to 1.0)
RFD200 Knee extension Affected side (Nm/Kg)	2.72(1.31)	3.16(1.27)	2.79(1.58)	2.66(1.44)	0.59(0.22 to 0.95)	0.4 (-0.1 to 0.8)
RFD200 Knee extension Unaffected side(Nm/Kg)	3.19(1.56)	3.53(1.58)	3.20(1.85)	3.13(1.59)	0.45(0.01 to 0.90)	0.3 (-0.2 to 0.7)
RFD200 Hip extension affected side (Nm/Kg)	3.56(2.56)	4.55(2.63)	3.52(3.05)	3.61(2.68)	1.07(0.19 to 1.97)	0.4 (-0.1 to 0.8)
RFD200 Hip extension unaffected side(Nm/Kg)	3.95(2.32)	4.47(2.03)	3.79(3.39)	3.76(2.95)	0.67(-0.04 to 1.37)	0.3 (-0.2 to 0.7)
Leg extension power						
Affected side (Watt/Kg)	1.5(0.6)	1.9(0.7)	1.4(0.7)	1.4(0.7)	0.4(0.2 to 0.5)	0.6 (0.2 to 1.1)
Unaffected side (Watt/Kg)	1.9(0.7)	2.2(0.8)	1.8(0.8)	1.7(0.8)	0.4(0.2 to 0.5)	0.5 (0.1 to 1.0)
Functional performance tests						
Stair climb ascending (steps/sec)	1.7(0.6)	2.0(0.7)	1.8(0.8)	1.8(0.8)	0.4 (0.2 to 0.5)	0.6 (0.1 to 1.0)
Stair climb descending (steps/sec)	1.9(0.8)	2.3(0.8)	2.0(1.0)	2.0(1.0)	0.4 (0.2 to 0.5)	0.4 (0.0 to 0.9)
Horizontal gait speed 20 m (normal) (m/sec)	1.2(0.2)	1.3(0.2)	1.2(0.3)	1.2(0.3)	0.1(0.1 to 0.1)	0.4(0.0 to 0.8)
Horizontal gait speed 20 m (max) (m/sec)	1.5(0.3)	1.7(0.4)	1.5(0.4)	1.5(0.4)	0.2(0.2 to 0.3)	0.6 (0.1 to 1.0)
Sit to stand x 5 (s)	14.5(5.4)	11.6(4.4)	15.1(6.9)	14.4(6.6)	-2.1(-3.2 to -0.9)	0.4(- 0.1 to 0.8)
Fat Free Mass						
Total fat free mass (Kg)	46.7(9.6)	47.1(9.7)	46.3(10.6)	46.1(10.5)	0.6(0.1 to 1.1)	0.1(-0.4 to 0.5)
Fat free mass femur affected side (Kg)	4.4(1.1)	4.5(1.2)	4.4(1.2)	4.3(1.2)	0.2(0.1 to 0.3)	0.2 (-0.3 to 0.6)
Fat free mass femur unaffected side (Kg)	4.5(1.1)	4.6(1.2)	4.5(1.2)	4.5(1.2)	0.1(0.1 to 0.2)	0.1 (-0.3 to 0.5)

*) Adjusted for baseline, sex, age and BMI.

Figure 9

Linear relationship in the intervention group between pre to post training changes in stair walk speed and changes in knee extension MVC (see text).





9. Discussion

9.1 Feasibility of preoperative explosive-type RT

Feasibility represents an important aspect of a clinical intervention. If a health care intervention is not well accepted by the study population, it will affect the clinical relevance (external validity) of the findings [92].

Pain in relation to preoperative exercise intervention in patients with late stage hip OA may affect the efficacy, however feasibility according to exercise related pain has only been inconsistently reported in previous preoperative exercise studies in relation to THA. During the present intervention with explosive-type RT, acceptable pain levels immediate after training (VAS≤5) were reported in 95% of all sessions. This indicates that prolonged intervention (10 weeks) of explosive RT of medium to high intensity is feasible in late stage hip OA patients scheduled for THA.

As expected for a group of untrained individuals, exercise induced delayed onset of muscle soreness was experienced following RT sessions. This was especially observed during the initial sessions as VAS >5 the following day was reported in approximately 1/3 of the sessions during the first 2 weeks. During the last 2 weeks of intervention the prevalence of pain the following day was as low as 6 %. Ageberg et al 2010 reported levels of acceptable immediate post exercise pain in 94 % of the sessions during preoperative neuromuscular exercises in patients with OA of the hip and knee, indicating the feasibility of the present intervention with high intensity explosive-type RT to be comparable with a lower intensity exercise intervention. Comparison of delayed onset muscle soreness between studies was not possible since 'pain the following day' was not reported in relation to neuromuscular exercise[135]; however, a higher level during the initial sessions would be expected with an RT intervention of the current intensity.

Participants in the intervention group shoved high adherence to training and no drop-outs were reported due to intervention. Moreover, no serious exercise related adverse events were reported. This is similar to previous studies of preoperative exercise therapy without explosive-type RT[62,78,79,141]. Good compliance (*a priori* defined adherence ≥ 80% of the sessions) was achieved by all participants who completed training (n=38 ~95%) which might be explained by low levels of exercise related pain, the intervention based on the concept of 'buddy-training' and the small training groups with dedicated physiotherapists.

9.2 Preoperative explosive-type RT – the patient reported outcomes

The effect of preoperative explosive-type RT on patient reported outcomes is currently unknown since this intervention has not previously been investigated in hip OA patients prior to THA. Previously, patient reported function and pain (HOOS or WOMAC) has been evaluated in four preoperative exercise studies with 'strengthening' exercises included in the intervention [62,78,79,142] of which only one study (Gilbey et. Al 2003) included exercises of progressive RT (however performed at slow velocities)[61]. Two studies[62,78] reported a significant effect in favour of exercise on self-reported function and no significant effect on pain (WOMAC) but the effect of the intervention (e.g. the between group difference at follow-up) was not reported in either of the two studies.

In the present study, a significant improvement in HOOS sub scale 'ADL function' (primary outcome) was observed in favour of intervention with an adjusted between-group difference at follow-up of 9.7 points, 95%CI (4.3 to 15.2)). Furthermore, the intervention group reported significant less pain (HOOS sub scale) compared to care-as usual with an adjusted between group difference at follow-up of 8.2 points, 95%CI (2.1 to 14.3).

A recent meta-analysis including preoperative exercise therapy widely defined as '*any* preoperative intervention containing flexibility, aerobic or strengthening exercise of more than one session in hip and knee replacement surgery', concluded exercise to have a medium effect size on patient reported pain and function [58] in hip OA patients waiting for surgery. A recent RCT evaluating preoperative neuromuscular training (without progressive RT) reported a medium effect size regarding both ADL function and pain prior to surgery; however the effects was not sustained 3 month after surgery[57,143]. In comparison we observed large effect size on ADL function (Cohen's *d*; 0.8) and a medium size effect (Cohen's *d*; 0.6) on pain in favour of 10 weeks with explosive-type RT.

Comparison and conclusions concerning the efficacy of interventions in the previous preoperative exercise studies are compromised by small sample sizes and vague descriptions of interventions [60]. Since the intervention period is a crucial aspect of the total exercise 'dose' it may also be of importance that all previous studies have shorter interventions (3 to 8 weeks) compared to the present 10 weeks. However, evidence is sparse regarding the 'adequate' intervention period for explosive-type RT (or other exercise interventions) to improve physical functioning.

In addition to the improvements in self-reported ADL function and pain, we observe significant effect in favour of intervention for the HOOS subscales 'symptoms', sport and recreation' and hip related quality of life with medium effect size (Cohen's *d*; 0.4 to 0.6). These subscales include information on perception of joint stiffness and instability, restrictions in strenuous physical functioning and the general satisfaction regarding the hip function.

Although potentially important, the general heterogeneity of the applied patient- reported outcomes hinder comparison between studies beyond ADL function and pain.

9.3 Preoperative explosive-type RT and muscle function

Despite the relation between leg muscle strength/power and limitations in physical functioning[34,100], the effect of preoperative explosive-type RT is unknown since enhancement of muscle function by explosive-type RT has exclusively been investigated as a post-operative intervention [54,80–82].

Except for one study (Gilbey et al 2003), previous studies of preoperative exercise have failed to provide evidence for any effect of preoperative exercise therapy on muscle function in hip OA patients scheduled for THA[62,63,78,79,143]. However, it is likely that insufficient loading (intensity of strengthening exercises when included), training volume (duration/frequency), progression, and/or compliance may explain the general lack of improvements in muscle strength reported in earlier studies since only one previous study qualify for the content of progressive RT[6158]. Gilbey et al, 2003 reported that 8 weeks of slow velocity progressive RT (as a part of a pre and post operative intervention)increased a combined leg strength score in the intervention group with a significant difference at preoperative follow-up ($p= 0.04$). However, the size of the effect (e.g. the between group difference at follow-up) was not reported.

In contrast, the present training protocol with explosive-type RT resulted in significant between-group differences in leg extension power and single joint isometric MVC for knee and hip extension in favor of intervention ($p<0.001$) with medium effect size (Table 6).

Despite leg muscle power has a stronger association with ADL functions than muscle strength[34,37,100], muscle power has only been reported in a single preoperative RCT from our group[57] . Villadsen et al (2014) investigated the effect of neuromuscular training (NEMEX) and found no significant effect on single joint muscle power or leg extension power at preoperative follow-up[143]. However, a significant effect in single joint muscle power (hip abduction/extension) but no effect on leg extension power was reported at 3 months follow-up after surgery [57].

Interestingly, the present findings regarding leg extension power following explosive-type RT prior to THA is comparable with explosive-type RT in healthy elderly without joint affection indicating that pain and physical impairment related to late stage hip OA does not affect the efficacy of the training intervention [77].

Suetta et al (2004) reported post- operative explosive-type RT to be superior to both conventional physiotherapy and neuromuscular electrical stimulation in the early rehabilitation phase, according to maximal muscle strength, explosive force characteristics (RFD) and functional performance measures indicating that explosive-type RT is effective to improve muscle function in the post-operative stage[54].

The present relative improvements in mean isometric MVC following the intervention (15%-22%), of the affected side appear slightly smaller than reported by Suetta et al (2004) (+ 24%) which might be due to a longer training period (12 weeks vs. 10 weeks) with a higher training volume (3 times/week vs. 2 times /week) may account for the higher effect on knee extension MVC observed by Suetta et al[54]. Furthermore, impaired range of motion and/or pain, presumable more frequently present in hip OA patients scheduled for surgery, may theoretically account for a reduced preoperative training effect. The feasibility according to immediate or delayed exercise related pain was not reported by Suetta et al, but the present findings of low levels of exercise related pain throughout the preoperative intervention indicate only a minor effect. Besides, since MVC on average improved equally between affected and unaffected leg in the present study, potential impaired joint function did not seem to affect the training effect for hip OA patients scheduled for THA.

The explosive force development in the initial phase of muscle contraction characterizes important aspects of muscle function in relation to strenuous ADL such as stair climb and the prevention of falling[34] of which both are important in a rehabilitation perspective. Nevertheless, explosive force characteristics of leg muscles (e.g. RFD 0-200 ms) have not previously been described in relation to preoperative exercise therapy.

The current training protocol was effective in improving explosive force characteristics (RFD 0-200ms) on the affected leg (Table 2). Surprisingly, the improvements in RFD were not retrieved on the unaffected leg. The observed improvements in explosive force characteristics on the affected leg may reflect changes in both neuromuscular activation (electromyogram (EMG) amplitude) [54] and/or cellular hypertrophy of fast twitch Type II muscle fibers[82]. However, it was beyond the limits of this thesis to include measurements of EMG and/or muscle morphology

9.4 Physical Functioning

Physical function improved significantly in IG compared to CG regarding all functional tests ($p<0.0001$) with largest effect size (Cohen's *d*; 0.6) observed in strenuous ADL functions (Stair climb ascending and horizontal maximal gait speed) whereas previous studies of preoperative exercise therapy have not resulted in improved objective measured physical functioning (e.g. stair climb or

gait speed) [62,63,78,79]. This might be explained by the improvements in muscle function following explosive-type RT since leg extension muscle function has been reported as a strong determinant for stair negotiation[34,71] .The lack of effect on physical capacity reported in previous studies of preoperative exercise therapy may reflect insufficient improvements in muscle function/strength as previously discussed.

9.5 Body Composition

Muscle atrophy is observed in late stage hip OA and presumable mainly related to impaired physical function [132]. The effects of exercise on changes in body composition (fat free mass) or other estimates of muscle mass/size has not previously been investigated in the context of preoperative exercise of hip OA patients scheduled for THA.

Significant between group differences in total body and regional (femoral) FFM (both sides) in favor of intervention were observed at follow-up ($p<0.013$). Although, an increase in fat free mass is not an aim *per se*, the observed changes following training are an indication of quantitative changes in muscle mass and efficiency of the intervention. A relative smaller gain in mean regional fat free mass (+2%) was observed compared with RT induced muscle hypertrophy reported in healthy elderly and in hip OA patients after THA (+5% to +12%)[35,54,66,144]. However, differences between methods used for quantifying muscle hypertrophy restrict comparison between studies and the effect size of the observed improvements was relatively small.

9.6 Associations between changes in muscle and ADL function

Only changes in MVC for knee extension (affected side) were associated with improvements in stair negotiation speed (ascending and descending), while changes in RFD (unaffected side) exclusively correlated to stair descending speed. Interestingly, Suetta observed only changes in RDF to correlated with improved physical function (changes maximum horizontal speed), with no correlation between increase in MVC and walking speed[54].

Our findings indicate that enhancement of the knee extensors in particular, are important for strenuous ADL in hip OA. In addition, faster stair negotiation may rely on improvements in both maximal strength and explosive force of the knee extensors.

9.7 Clinical implications

The present findings show that progressive explosive RT is feasible in patients with hip OA scheduled for THA and significantly increases self reported ADL function by 9.7 points compared with CG (p=0.001), which is in accordance with previously studies using 10 points as a 'clinically relevant' difference[57]. A change of 7.9 on the WOMAC 'function' (identical to HOOS ADL function) has been reported as a 'minimal clinical important improvement' for hip OA patients in medical treatment with NSAID[97]. However, these finding may not be applicable for patients scheduled for surgery. Nonetheless, with a larger effect size compared to previous preoperative exercise studies [58] the present improvements in ADL function may sustain the impact of surgery and translate into improved postoperative outcome.

In a clinical perspective augmenting leg muscle strength prior to surgery may be an important target of intervention since low muscle strength prior to surgery, has been reported as a predictor for poor post-operative ADL function [30]. This study indicates that muscle strength in hip OA patients scheduled for THA respond to explosive-type RT and the improvements are related to significant better physical functioning during strenuous ADL tasks. These findings may have important implications for improved post-operative recovery of functional tasks. For isolated muscle groups, only changes in maximal isometric muscle strength and explosive force characteristics of the knee extensors were associated with the improvements in physical functioning. Relationship between improvements in knee extension muscle strength and enhanced physical functioning were found for both legs. The latter observations may be of relevance for efficient targeting of training interventions in future regimens.

Importantly, following the intervention MVC and RFD outcomes of the affected leg leveled the baseline measurements of the unaffected leg (Table 2). Thus, the present data indicate that 10 weeks of explosive-type RT prior to surgery may recover OA related deficits in muscle strength.

Finally, performing sustained, frequent high intensity RT may theoretically pose a risk of increased cartilage wear over time in hip OA patients. However, the loading time during each contraction during explosive-type RT is very short and in the current exercise protocol a maximum of 36 repetitions (3 series with a maximum of 12 repetitions each) is performed in 4 exercises for a limited time period (20 sessions). Furthermore, all exercises were performed in a sitting position were the joint compression forces are reduced. Thus, it may not be comparable to the cumulative load during daily activities like walking and stair climb. In addition, this study does not indicate worsening of patient-reported symptoms following the intervention. Still, possible risk of harms should be considered before implementation of prolonged high intensity RT protocols in hip OA patients not scheduled for joint replacement surgery.

10. Conclusion

In this thesis the intervention with progressive explosive-type RT as a preoperative therapy for patients with hip OA was investigated regarding its feasibility and the preoperative efficacy regarding functional disability, pain and muscle function. To my best knowledge intervention with progressive explosive-type RT of medium to high intensity has not previously been investigated in hip OA patients scheduled for THA.

We have shown that patients with symptomatic hip OA scheduled for THA can comply with medium to high intensity RT in aspects of adherence, exercise-related pain and harms. This is an important finding since previous reports on limited effect of preoperative exercise may rely on insufficient intensity of the exercise programs.

The present intervention significantly improved self reported outcomes including function, pain, symptoms and hip related quality of life compared to care-as-usual. The effect sizes of improvements in self-reported function indicate that progressive explosive-type RT of medium to high intensity twice a week for a period of 10 weeks is an effective intervention for improving ADL function prior to surgery. In addition the intervention was effective to enhance leg muscle function (strength/power) and physical functioning in hip OA patients. Increased total and regional (femoral) fat free mass was observed as well, indicating leg muscle hypertrophy. Positive associations between improvements of knee extension muscle strength and stair negotiation indicates knee extension strength to be an important target for rehabilitation of physical function in hip OA.

In perspective, the present study holds promise for an accelerated or even improved post-surgery rehabilitation.

11. Perspectives and future research

The findings presented in this thesis have perspectives regarding management of both pre and post operative stages in the clinical pathway of hip OA patients.

Preoperative: The effect size of preoperative explosive-type RT on functional status and pain generates the question if this exercise intervention have indications regarding postponing or even cancelling surgery for some patients. However, this was not within the framework of the research question initially posed and therefore not included in the present thesis but it will be attended in

future research[145]. The issue is closely related to the term 'patient acceptable symptom state' which is highly relevant to address when designing future preoperative intervention studies in OA [97,146].

The in-hospital stay: Preoperative conditioning of muscle function with explosive-type RT may prove its relevance as an adjunct therapy for improving immediate postoperative mobility. In particular fast track surgery may benefit from patients with better preoperative functioning which should be attended in future research. An improved preoperative functional status may translate to faster recovery, leading to shorter admission times. In future studies a full scale socioeconomic evaluation regarding the cost effectiveness of preoperative RT is warranted.

Postoperative: The present findings hold promise for a better postoperative rehabilitation. The future perspectives regarding potential benefits for the early (3 month follow-up) and late (1 year follow-up) post operative rehabilitation will be attended when the postoperative data of the current RCT is collected and analyzed. However, potential benefits of preoperative RT regarding quantification of the need of out-patient rehabilitation services and general independence in ADL (e.g. the use of walking aid during rehabilitation) is not included and should be addressed in future studies.

In the patient's perspective, the waiting time to surgery is important and future research should attend the dose of the intervention since the current study does not indicate the adequate duration and frequency of a preoperative explosive-type RT intervention. Furthermore the potential an additive effect of mixed interventions (e.g. with neuromuscular training) should be observed since both interventions have been reported feasible and effective for improvement of physical function in hip OA.

Finally; the group training design with a limited number of physiotherapists necessitated the exclusion of the most functional impaired patients in the present study. Future preoperative intervention studies with RT should be designed to engage the most functional impaired patients in particular, since this patient category may benefit the most from functional improvements.

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13. Summery

Osteoarthritis (OA) of the hip is a degenerative joint disease characterized by loss of joint cartilage in the hip joint. In symptomatic hip OA are the most common symptoms of pain and disability. Decreased muscle strength / function and muscle atrophy in the affected leg is found in patients with hip OA which may affect postoperative functional level. Furthermore is the physical capacity (e.g. walking speed and climbing stairs) affected in hip OA. Pain-related decreased daily function leading to decreased activity believed to contribute to the observed loss of muscle function and muscle mass. However, the evidence of hip patients' actual activity level is decreased compared to healthy elderly is limited because of few number of studies and lack of validation of the objective measures of physical activity in the patient group.

Previous preoperative training studies have found no evidence of effect on objectively measured physical function (eg walking speed) or muscle strength and found only a moderate effect on self - assessed function and pain. However, these studies are generally characterized by small populations and large variation in the type of intervention.
There is considerable evidence for the effectiveness of heavy resistance of explosive type to improve muscle function, muscle mass and physical function parameters in healthy elderly. Similar results are found in hip OA patients following postoperative intervention. Despite this, the effect of heavy explosive strength training has not previously attempted studied in hip OA patients as preoperative intervention.
In this thesis I wish, therefore, to answer the question of heavy explosive strength training is effective and feasible as preoperative intervention in a population of hip OA patients scheduled for THA.
The patient's self-reported functional capacity is selected as the primary endpoint. In addition we examined self-reported pain, symptoms, sports and recreational function and hip related quality of life.
To evaluate changes in physical function capacity selected a battery of objective physical function tests consisting of climbing stairs, horizontal walk and 5 x repeated chair rise test. Muscle function is evaluated as extension power measured by leg extension and isolated isometric muscle strength (maximum strength and initial explosive strength) by hip and knee extension, respectively, since both leg extension power and muscle strength correlates with daily functions such as e.g. climbing stairs. For the comparison to previous studies of heavy explosive strength regarding changes in muscle mass (exercise - induced hypertrophy), changes in fat free mass was measured by means of DEXA. Finally we wished to validate a method for objectively measured activity level in the patient group to apply this outcome as an additionally exploratory outcome in the intervention study.
In chronological order, the first two (method) studies was dealing with 1) the validity of objectively measured activity in patients with hip OA and 2) the reproducibility of the selected physical function tests and muscle function / strength test .
Study 1: Objectively measured activity using activity meters have not been previously validated in patients with hip OA. A body-worn activity monitor was selected based on ease of use, commercial availability and reported acceptable validity in healthy adults and healthy elderly. The activity monitor

was validated during a 2-hour scenario consisting of simulated ADL functions and rest. Twenty hip OA patients (10 preoperative, 10 postoperative) completed the scenario and the estimated level of activity was validated against simultaneously measured energy expenditure by indirect calorimetry (gold standard) . The error measurement (bias) compared to indirect calorimetry varied between -25 % and + 180% depending on the activity type and the variance varied between methods so we concluded that the method is not currently valid to asses changes in activity level within a longitudinal cohort of hip OA patients and the outcome was not applied in intervention studies.

Study 2: Before the start of the intervention study, the reproducibility of the selected outcomes for physical function and muscle function was implemented as a test -retest study in a cohort of 13 hip OA patients scheduled for THA with identical inclusion criteria as the intervention study. Physical function tests of muscle function tests showed moderate to good agreement and good to excellent reliability with poorest reliability and agreement observed in the muscle function tests.

Study 3: The inclusion of patients took place between April 2010 and June 2011. A cohort of 80 patients were included (mean age 70.4 years, 65% women) and randomized (1:1) into 2 groups. Sample size was calculated based on a clinically relevant effect on the primary outcome. The intervention group completed 10 weeks of preoperative training, 2 X weekly supervised by trained physiotherapists. The training consisted of 4 training stations with a focus on training the hip and thigh muscles (flexion / extension) and was performed in 3 sets of 8-12 repetitions . Continuous progression of the load was secured by physical therapists. The control group followed the standard pre-operative course.

Feasibility was assessed on adherence to exercise (the proportion of complete training sessions in relation to the maximum possible) , drop- outs , side effects and training related pain . We found high compliance (93%) , few drop- outs (none related to the intervention) , few small training -related side effects, including low exercise -related pain, We could therefore conclude that heavy explosive strength training was feasible in a population of hip OA patients scheduled for THA.

Regarding the effects, we found that intervention with10 weeks of progressive explosive esistance training improved self- evaluation function (primary outcome) as well as pain, symptoms and hip related quality of life , relative to the control group . The intervention group improved muscle function (leg power and maximum isometric function) , physical function (horizontal walking speed, stair climb and sit- stand) and increased muscle mass compared to the control group.

In conclusion; preoperative heavy explosive strength training for 10 weeks before THA is feasible and safe in patients with hip OA with a significant effect on both self- evaluation function and pain as well as objectively measured function and muscle function. In relation to post-operative recovery, the present findings of a significant preoperative effect on physical capacity , muscle function, muscle mass aspires for improved postoperative rehabilitation

14. Dansk resume

Hofteartrose er en degenerativ ledsygdom kendetegnet ved tab af ledbrusk i hofteleddet. Ved symptomgivende hofteartrose er de hyppigste symptomer smerter og nedsat funktion. Hos patienter med symptomgivende hofteartrose finder man nedsat muskelstyrke/funktion og muskelatrofi i det afficerede ben med betydning også for postoperativt funktionsniveau. Endvidere findes den fysiske kapacitet (f. eks ganghastighed ved alm. gang og trappegang) nedsat. Smertebetinget nedsat daglig funktion ledende til nedsat aktivitet menes at bidrage til det observerede tab af muskelfunktion og muskel masse. Viden om hoftepatienters faktiske aktivitetsniveau i forhold til raske er imidlertid begrænset grundet få studier samt manglende validering af at objektive målemetoder for fysisk aktivitet i patientgruppen.

Tidligere præoperative træningsstudier har ikke fundet evidens for effekt på objektivt målt fysisk funktion (f. eks ganghastighed) eller muskelstyrke og kun fundet moderat effekt på selv-evalueret funktion og smerte. Dog er disse studier kendetegnet ved små populationer og stor variation i interventionstype.

Der er betydelig evidens for effektiviteten af tung styrketræning af eksplosiv type til forbedring af muskelfunktion, muskelmasse samt fysiske funktions parametre i raske ældre. Tilsvarende resultater er fundet hos hofteartrose patienter som postoperativ intervention. På trods af dette er effekten af tung eksplosiv styrketræning er ikke tidligere forsøgt undersøgt i hofteartrosepatienter som præoperativ intervention.

I denne afhandling ønsker jeg derfor at besvare spørgsmålet om tung eksplosiv styrketræning er effektiv og gennemførlig som præoperativ intervention i en population af hofteartrose patienter planlagt til THA.

Patientens selvrapporterede daglige funktionsniveau er valgt som primære effektmål. I tillæg undersøges selvrapporteret smerte, symptomer, sport og rekreativ funktion samt hofte relateret livskvalitet. Til evaluering af ændringer i fysisk funktionskapacitet er udvalgt et batteri af objektive fysiske funktions tests bestående af trappegang, horisontal gang og 5 x gentaget rejse sig fra stol test. Muskelfunktion er evalueret som ekstensions power målt ved ben ekstension samt isoleret isometrisk muskelstyrke (maximal styrke og initial eksplosiv styrke) ved hhv. hofte og knæekstension da ben ekstensions power og muskelstyrke korrelerer til daglige funktioner som f eks trappegang. For sammenlignelighed til tidligere studier af tung eksplosiv styrketræning, er der tillige søgt redegjort for ændringer i muskelmasse (træningsinduceret hypertrofi) ved hjælp af måling af kropssammensætning (DXA scanning). Tillige ønskede vi at validere en metode for objektivt målt aktivitetsniveau i patientgruppen mhp en evt. inkludering af dette outcome som eksplorativt effektmål for interventionens effekt på aktivitetsniveauet.

I kronologisk rækkefølge er de første to studier metodestudier omhandlende 1) validitet af objektivt målt aktivitetsniveau hos patienter med hofteartrose 2) reproducerbarheden af de valgte fysiske funktionstest og muskelfunktion/styrketest.

Studie 1: Objektivt målt aktivitetsniveau ved hjælp af aktivitetsmålere er ikke tidligere blevet valideret hos patienter med hofteartrose. En kropsbåren aktivitetsmåler blev udvalgt på baggrund brugervenlighed

samt rapporteret acceptabel validitet hos raske voksne samt raske ældre. Aktivitetsmåleren blev valideret under et 2 timers scenarie bestående af simulerede ADL funktioner og hvile. Tyve hofteartrose patienter (10 præoperative, 10 postoperative) gennemførte scenariet og det estimerede aktivitetsniveau blev valideret i forhold til simultant målt energiomsætning ved indirekte calorimetri (guld standard). Med fejlmåling (bias) i forhold til indirekte caloriemtri på mellem –25% og +180 % afhængig af aktivitets typen samt betydelige aktivitetsafhængige udsving i variansen, konkluderede vi at metoden ikke på nuværende tidspunkt er valid som måleinstrument for aktivitet i en longitudinel hohorte af hofteartrose patienter, hvorfor den efterfølgende udgik som effektmål i interventionsstudiet.

Studie 2: Inden påbegyndelse af interventionsstudiet blev reproducerbarheden af de valgte effektmål for fysisk funktion samt muskelfunktion blev gennemført som test-retest studie i en kohorte af 13 hofteartrosepatienter planlagt til THA med identiske inklusionskriterier som interventionsstudiet. Fysiske funktionstest of muskelfunktions tests udviste moderat til god overensstemmelse (agreement) og god til excellent pålidelighed med lavest pålidelighed og agreement i muskelfunktions tests.

Studie 3: Inklusionen af patienter foregik mellem april 2010 og juni 2011. En kohorte på 80 patienter blev inkluderet (middelalder 70.4 år, 65% kvinder) og randomiseret (1:1) til 2 grupper. Gruppestørrelsen var beregnet ud fra en klinisk relevant effekt på det primære effektmål. Interventionsgruppen gennemførte 10 ugers præoperativ styrketræning, 2X ugentligt superviseret af trænede fysioterapeuter. Træningen bestod af 4 stationer med fokus på træning af hofte og lår muskulaturen (fleksion/ekstension) og blev udført i 3 serier af 8-12 gentagelser. Kontinuerlig progression af belastningen blev sikret af fysioterapeuter efter protokol. Kontrolgruppen fulgte det præoperative standardforløb.

Gennemførlighed blev vurderet på compliance til træningen (andelen af gennemførte træningssessions i forhold til maximalt mulige), drop-outs, bivirkninger samt træningsrelateret smerte. Vi fandt høj compliance (93%), få drop-outs (ingen med relation til intervention), få og små træningsrelaterede bivirkninger herunder lav træningsrelateret smerte og kunne derfor konkludere at tung eksplosiv styrketræning er gennemførlig i en population af hofteartrosepatienter der venter på THA.
I forhold til effekt fandt vi at intervention med tung eksplosiv styrketræning forbedrede selvevalueret funktion (primære effektmål) såvel som smerte, symptomer og hofterelateret livskvalitet i forholdt til kontrolgruppen. Interventionsgruppen forbedrede muskelfunktion (ben power og maksimal isometrisk funktion), fysisk funktion (ganghastighed ved horisontal- og trappegang og sit-stand) og øgede muskelmasse i forhold til kontrolgruppen.
Man kan således konkludere at præoperativ tung eksplosiv styrketræning i 10 uger inden THA er gennemførlig og sikker hos patienter med hofteartrose med signifikant effekt på både selvevalueret funktion og smerte samt objektivt målt funktion og muskelfunktion. I forhold til postoperative forløb giver dette studies fund af effekt på fysisk kapacitet, muskelfunktion, muskelmasse forhåbninger om forbedret postoperativt rehabiliteringsforløb.

15. Papers

Paper 1

BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

Low validity of the Sensewear Pro3 activity monitor compared to indirect calorimetry during simulated free living in patients with osteoarthritis of the hip

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Abstract

Background: To validate physical activity estimates by the Sensewear Pro3 activity monitor compared with indirect calorimetry during simulated free living in patients diagnosed with osteoarthritis of the hip pre or post total hip arthroplasty.

Methods: Twenty patients diagnosed with hip osteoarthritis (10 pre- and 10 post total hip arthroplasty; 40% female; age: 63.3 ± 9.0; BMI: 23.7 ± 3.7). All patients completed a 2 hour protocol of simulated free living with 8 different typical physical activity types. Energy consumption (kcal/min) was estimated by the Sense Wear pro3 Armband activity monitor and validated against indirect calorimetry (criterion method) by means of a portable unit (Cosmed K4b^2). Bias and variance was analyzed using functional ANOVA.

Results: Mean bias during all activities was 1.5 Kcal/min 95%CI [1.3; 1.8] corresponding to 72% (overestimation). Normal gait speed showed an overestimation of 2.8 Kcal/min, 95%CI [2.3; 3.3] (93%) while an underestimation of -1.1 Kcal/min, 95%CI [-1.8; -0.3] (-25%) was recorded during stair climb. Activities dominated by upper body movements showed large overestimation with 4.37 Kcal/min, 95%CI [3.8; 5.1] (170%) being recorded during gardening. Both bias and variance appeared to be dependent on activity type.

Conclusion: The activity monitor generally overestimated the energy consumption during common activities of low to medium intensity in the patient group. The size and direction of the bias was highly dependent on the activity type which indicates the activity monitor is of limited value in patients with hip osteoarthritis and that the results do not express the real energy expenditure.

Background

Patients with osteoarthritis (OA) of the hip have excess all cause mortality including increased mortality related to cardiovascular disease which has been associated with reduced patient reported physical activity (PA) [1]. Studies indicate that a majority of patients with lower extremity OA may not meet general recommendations regarding PA [2]. However, as the same is evident for the elderly population in general [3] it is still uncertain to which extend the functional impairment and pain present in symptomatic hip OA affects the actual PA compared with the general population. Studies of the objectively measured PA in patients with hip OA and total hip arthroplasty (THA) are limited especially regarding comparison with healthy controls [4-6] and their results are restricted by the general lack of validation studies of the used data collecting tools applied in patients with degenerative joint disease. Thus, establishing knowledge of the validity of objective measured PA in hip osteoarthritis patients is of importance for future research.

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PA is defined as any bodily movements produced by skeletal muscles that require energy expenditure [7]. Energy expenditure during PA is commonly investigated by indirect calorimetry which requires either isolation of individuals in closed spaces or portable apparatus for gas analysis of air exchange [8,9]. These methods are often referred to as criterion methods [10] but their application is limited to small laboratory settings [8,9]. In free living small body-worn multisensory activity monitors based on accelerometry can be used as a feasible surrogate measure of energy expenditure during PA [11-13]. In clinical studies such activity monitors are applied due to their objectivity compared to self-reported physical activity questionnaires [5,14] and they may become a tool in future etiological and prognostic studies in patients with lower extremity osteoarthritis [15]. However, in hip OA patients altered movement patterns may occur [16,17] and functional impairment and pain may affect the speed of exercises both potentially affecting estimations of energy expenditure based on accelerometry.

In the current study the Sensewear pro3 (SWA) activity monitor armband was validated. The SWA is a small multisensory activity monitor that combines accelerometry with various physiological data (see Method; Equipment). The monitor requires minimal instruction in use which suits the application in free living studies. The outcome in terms of energy expenditure is readily comparable with recommendations for PA (e.g. The American College of Sports Medicine [18]). Recently, the SWA has been used in a various clinical studies of actual PA in different patient groups [14,19-23] and in OA patients the monitor has been applied in a comparable study of PA between patients with hip and knee OA and healthy controls [5]. However, like other activity monitors the validity in this patient group is unknown. Varying degrees of bias has been observed when validated in healthy older adults [11,24], obese adults [25] and in various patient groups including patients with rheumatoid arthritis [13,26-28]. In healthy adults the SWA been reported reliable [25,29] and valid for estimation of cumulated daily energy expenditure [12,30]. However, limitations regarding validity has been reported during various activity types [31-34].

The purpose of this study was to investigate the validity of the SWA activity monitor in patients with hip osteoarthritis during a simulated free living protocol according to the following 3 proprieties: i) Bias between activity monitor estimates and indirect calorimetry (criterion method), ii) correlation between methods and iii) difference in variance [35].

Method

Participants

A convenience sample of 20 patients (10 of preoperative stage, 10 of postoperative stage) diagnosed with hip OA (Gender: 40% female, Age: 63.3 ± 9.2 years, BMI: 23.7 ± 3.8) treated with THA or scheduled for THA at the Department Orthopaedic Surgery and Traumatology, Odense University Hospital (12 males, 8 females), were included.

Inclusion/exclusion

Inclusion criteria for the preoperative group: Diagnosed primary OA of the hip and scheduled for surgery (THA).

Inclusion criteria for the postoperative group: Diagnosed primary OA of the hip, treated with THA within 6 to 12 months of inclusion.

Exclusion criteria (both groups): Patients with a known history of symptomatic lung or heart disease or known symptoms of claustrophobia or unease using a mask and patients not understanding Danish language were excluded. Patients dependent on walking aid (and therefore unable to comply with the free living protocol) were excluded as well. Finally, for the post surgery group, patients with a scheduled reoperation of the hip or previous dislocation were excluded.

Twenty five were asked, 3 declined to participate and 1 was excluded due to known symptomatic lung disease and 1 due to known symptoms of claustrophobia. All 20 participants were able to complete the free living scenario.

All participants gave informed written consent and the conditions and methods of the study protocol was approved by the Ethical Committee, Region of Copenhagen, Denmark (Identifier; H-2-2010-47) and performed in accordance with the Helsinki Declaration of 1975, as revised in 2000.

Equipment

The activity monitor:

A small multisensory activity monitor (Sensewear Pro3 armband (SWA)) was positioned over the triceps brachii muscle of the right arm at the midpoint between the acromion and olecranon processes (size; 85.3 mm × 53.4 mm × 19.5 mm). The activity monitor collects physiological data from following sensors; a 2 axial accelerometer, a heat flux sensor, a skin temperature sensor, a near body ambient temperature sensor, and a galvanic skin response sensor. The activity monitor uses an onboard algorithm (InnerView TM Professional software version 5.1.0) fitted with anthropometric data from the participant (gender, age, height, and weight). The output is energy expenditure (kcal/min) calculated by an internal inaccessible algorithm.

Criterion Method:

Indirect calorimetry: For validation of the SWA armband a portable metabolic monitor (Cosmed model $K4b^2$) was worn during the protocol. The $K4b^2$ weighs 1.5 kg including a battery and is mounted on the chest with a simple harness. The $K4b^2$ has been shown valid in comparison to Douglas bag method [36]. Prior to the study

the apparatus had been serviced by the manufacture and validated against Douglas Bag by the authors (Data not shown). Before each test, the monitor was calibrated in accordance with the manufactures instructions. Energy expenditure (kcal/min) was calculated from the breath-by-breath oxygen use and carbon monoxide production.

Study protocol

A two hour protocol of 8 activities of daily living was designed. Activities imitate common activities of daily living expected for the patient/age group. Activities were: I) rest; 53 minutes (which includes all periods of rest in sitting and supine position), II) a simple warm-up program with steps and multi-planar movements; 9 minutes, III) sitting and walking between chairs; 4 minutes, IV) ascending and descending stairs; 4 minutes (4 steps, step height 15 cm), V) walking; normal; 15 minutes (self-paced) and brisk walking; 10 minute, VI) jogging; 5 minutes (or brisk walking), VII) outdoor gardening; 10 minutes (raking), and VIII) indoor cleaning; 10 minutes (sweeping floor).

All activities were supervised and performed in a consecutive order following the protocol without time breaks or discontinuity of measurements. Participants were instructed to perform the activities within the intensities of their daily living. If an activity was impossible to perform due to pain or impairment of hip movements a lower intensity level was selected and the alteration was registered.

Subjects were fasting and refrained from smoking and drinking coffee 1 hour prior to testing to diminish possible influence on the basic energy expenditure. Before each assessment, the activity monitor was initialized and fitted to the patient according to the manufacturer's instruction. The data was downloaded in 1 minute epochs by software provided by the manufacturer (InnerView Professional Research Software Version 5.1.0).

The K4b2 was calibrated and mounted on the participant. For acclimatization the subjects rested seated 10 minutes prior to the protocol. To identify the time periods of the individual activities during the later data analysis both units (the SWA and the K4b2) and the time scheme of the protocol were synchronized by an electronic clock. The validation procedure including the initial calibration of units was performed by the principal author.

Data analysis

Bias was defined as the difference between the activity monitor and indirect calorimetry outcomes (kcal/min). Activity specific bias was analyzed for each activity separately (the 15 time intervals coded #1-#15). To diminish possible carry over effects between intervals due to VO_2 latency, the first minute of each interval (#1-#15) was excluded from the later mean bias analysis of each activity and intervals of 2 minutes and less (interval #3 and #5) were regarded non-conclusive results. Mean bias of all 15 intervals (#1-#15) are presented.

Statistical analysis

Statistical analysis was carried out using functional data analysis [37]. This approach treats an entire curve of observations as a single datum rather than a collection of separate observations. In the present context each time dependent trajectory of the activity monitor and indirect calorimetry represents an observation. The techniques allow for a flexible characterization of the dynamics with minimal assumptions. In contrast, traditional methods such as linear mixed models that are based on the individual time points impose a parameterization on the functional form of the mean.

Specifically, we are interested in estimating the first two functional moments of the data. The functional mean leads to the definition of a time dependent bias function that varies freely over durations of the activities.

From the second order moments the functional variance processes [38] and the correlation coefficient were estimated [39] where the former characterize the internal stability of the activity monitor and indirect calorimetry.

The first step was to project the observed data into function space. We used a cubic b-spline basis with a knot placed at every minute and a data adaptive roughness penalty on the second derivative. The penalty parameter was estimated using the generalized cross-validation criterion [37].

A two-way functional ANOVA model showed no significant effect of surgical status, thus this factor was removed and the following results are based on pooled data.

The bias function was estimated as the functional mean of the pair-wise differences between the activity monitor and the indirect calorimetry curves with corresponding 95% confidence bands estimated by the method described by Cuevas et al. (2006) using the L2 norm as proximity measure [40].

The mean and relative biases of each interval (#1-#15) was calculated by a numeric quadrature rule over the corresponding intervals and the confidence intervals were based on a pair-wise re-sampling procedure.

Statistical analysis was carried out using R version 2.15.2 (2012-10-26) "Trick or Treat" Copyright (C) 2012 The R Foundation for Statistical Computing ISBN 3-900051-07-0.

Results

Descriptive characteristics of subjects are shown in Table 1.

All participants completed the protocol and all activities were performed according to the protocol except during activity #13 in which all participants declined to perform jogging due to self esteemed lack of physical capability. Brisk walking was performed instead.

Table 1 Subject characteristics

	Total (n = 20)	Female (n = 8)	Male (n = 12)
Age (years)	63.3 ± 9.2	67.1 ± 8.6	60.7 ± 9.0
Weight (kg)	82.8 ± 15.0	73.4 ± 11.2	89.0 ± 14.3
Height (m)	174.2 ± 7.7	167.8 ± 5.2	178.5 ± 5.9
BMI (kg/m^2)	23.7 ± 3.8	21.9 ± 3.3	24.9 ± 3.8

Data are $\bar{x} \pm$ SD.

Figure 1 illustrates the mean bias (difference) between the SWA and indirect calorimetry as a continuous time function with 95% confidence intervals. The bias is mainly significant positive (overestimation) with a fluctuant pattern that appears to follow transitions in activity mode.

The total energy expenditure was overestimated by 72% by the SWA during giving a significant average overestimation of 1.5 Kcal/min, 95%CI (1.3,1.8) during all activities (Table 2).

During walking activities (#8, #11, #13) overestimation ranged between 62% and 93%. Significant underestimation (-25%) was observed during ascending/descending stairs (#6) while intervals dominated by upper body movement (#9 and #15) showed large overestimation of 170% and 119% for outdoor gardening and indoor cleaning, respectively (Table 2).

Figure 2 illustrates the variance processes of the two methods and demonstrates the SWA to be less stable during most activities except for periods of resting. The correlation coefficient between methods (all activities) was 0.94.

Discussion

In the present study the SWA activity monitor was validated during simulated activities of daily living in a group of patients with hip osteoarthritis before or after THA by means of indirect calorimetry. The main findings were significant overestimations of energy expenditure by the activity monitor of up till 170% during common activities of daily living. Bias and variance showed dependency on the type of activity performed.

The SWA has been used for estimation of PA in various patient groups including patients with hip and knee OA [5,14,19-23]; however, to our knowledge no previous studies have investigated the validity of the SWA or other activity monitors in patients with OA of the hip. The majority of validation studies of have been conducted in healthy adults [12,30-34,41] of which two studies have reported the SWA as a valid tool for estimation of cumulated daily energy expenditure in comparison with doubly labeled water [12,30]. This contrasts with the majority of the activity specific protocols (using indirect calorimetry as criterion method) reporting the validity to be dependent of both the intensity and type of activity [31,33,34,41,42]. Direction of bias during walking activities may change according to inclination [34] and overestimation has been reported during exercise of the upper extremities [31]. This is in correspondence with the current findings of underestimation during stair climbing activities and overestimation during horizontal walking and in activities dominated with upper body movements. In healthy elderly numbers of validation studies are few and inconclusive in particular regarding the validity during activities [11,24]. In a study of resting energy expenditure in healthy

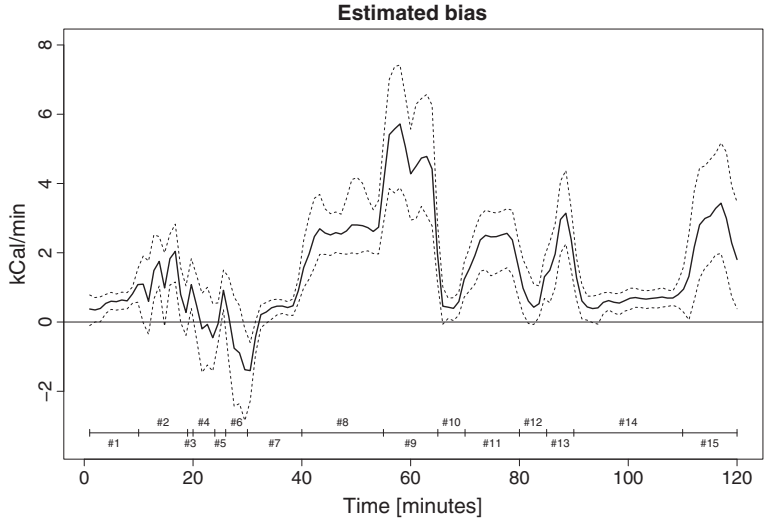

Figure 1 Bias between Sensewear Pro3 (SWA) estimates and indirect calorimetry (gold standard). Bias expressed as the mean difference with 95% confidence intervals. The horizontal line represents no difference between the methods. A positive value represents an overestimation of SWA. Coding #1-#15 represents intervals of steady state activity (see Table 2).

Table 2 Activity types of the protocol with coding for intervals

Activity type	Length (min)	Interval	EE SWA (kcal/min)	EE IC (kcal/min)	Bias (kcal/min)	Bias (%)
Total	**120**		**3.7 [3.4; 4.0]**	**2.2 [1.8; 2.6]**	**1.54 [1.3; 1.8]**	**71.8 [51.7; 92.8]**
Resting in chair	10	#1	1.5 [1.4; 1.6]	0.9 [0.7; 1.1]	0.6 [0.5; 0.8]	77.8 [45.2; 117.5]
Work out (steps and multi planar movements)	9	#2	4.2 [3.8; 4.6]	3.0 [2.5; 3.5]	1.2 [0.7; 1.6]	40.3 [21.0; 60.8]
Resting in chair[2]	1	#3	3.0 [2.6; 3.4]	2.3 [1.9; 2.7]	0.7 [0.1; 1.2]	29.6 [5.4; 57.3]
Sitting/standing and walking between 2 chairs	4	#4	3.6 [3.1; 4.1]	3.8 [3.2; 4.4]	-0.2 [-0.8; 0.4]	-4.7 [-19.6; 10.5]
Resting I chair[2]	2	#5	2.6 [2.0.; 3.1]	2.1 [1.6; 2.5]	0.5 [0.1; 1.0]	27.0 [2.4; 59.3]
Stair climbing (5 steps up/down)	4	#6	3.1 [2.7; 3.6]	4.2 [3.6; 4.9]	-1.1 [-1.8; -0.3]	-24.8 [-39.1; -7.6]
Resting in a supine position	10	#7	1.5 [1.3; 1.6]	1.0 [0.8; 1.2]	0.5 [0.3; 0.7]	53.1 [25.6; 81.0]
Walking normal speed (self paced)	15	#8	5.8 [5.1; 6.5]	3.0 [2.5; 3.5]	2.8 [2.3; 3.3]	93.3 [72.0; 119.1]
Outdoor gardening (raking leaves)	10	#9	7.0 [6.1; 7.8]	2.6 [2.2; 3.1]	4.4 [3.8; 5.1]	170.3 [134.0; 211.4]
Resting in chair	5	#10	1.8 [1.6; 2.0]	1.0 [0.8; 1.3]	0.8 [0.5; 0.9]	73.9 [42.5; 105.7]
Brisk walking	10	#11	5.7 [5.2; 6.2]	3.5 [2.9; 4.1]	2.2 [1.7; 2.6]	62.9 [42.3; 87.2]
Resting in chair	5	#12	2.1 [1.8; 2.4]	1.2 [1.0; 1.5]	0.9 [0.6; 1.2]	71.8 [41.3; 107.7]
Jogging/brisk walking	5	#13	6.1 [5.2; 7.2]	3.8 [3.1; 4.5]	2.3 [1.8; 2.9]	61.9 [45.3; 81.9]
Resting in chair	20	#14	1.4 [1.3; 1.5]	0.8 [0.6; 1.0]	0.7 [0.5; 0.8]	88.0 [47.2; 136.2]
Sweeping floor	10	#15	5.0 [4.2; 5.8]	2.3 [1.9; 2.8]	2.7 [1.9; 3.5]	119.4 [75.0; 172.1]

Mean values of energy expenditure (EE) measured by Sensewear Pro3 (SWA) and indirect calorimetry (IC) and absolute and relative bias between units[1]. Positive bias values indicate overestimation of SWA.
[1]Values are $\bar{x}$ with 95% confidence interval.
[2]Regarded as non conclusive due do short time period (see text).

elderly individuals (age (years); males 67.9 ± 5.1, females 69.2 ± 5.1) Heiermann et al. (2011) found an overestimation (12-14%) compared to indirect calorimetry [24] while Mackey et al. (2011) reported the SWA to be a valid tool for estimation of cumulated daily energy expenditure compared to doubly labeled water. Activity specific protocols in healthy elderly are currently lacking. In our population (age (years); 63.3 ± 9.2) we observed overestimation during rest and in the majority of activities (Table 2). Despite difficulty in comparison between studies the observed bias in the current study of hip OA patients appears larger than observations in healthy adults [31,33,34,41,42]. Meanwhile, recent validation studies in different elderly patient groups have indicated overestimation during various activities [27,28]. In elderly diabetic patients reported overestimations between 78% and 81% was reported

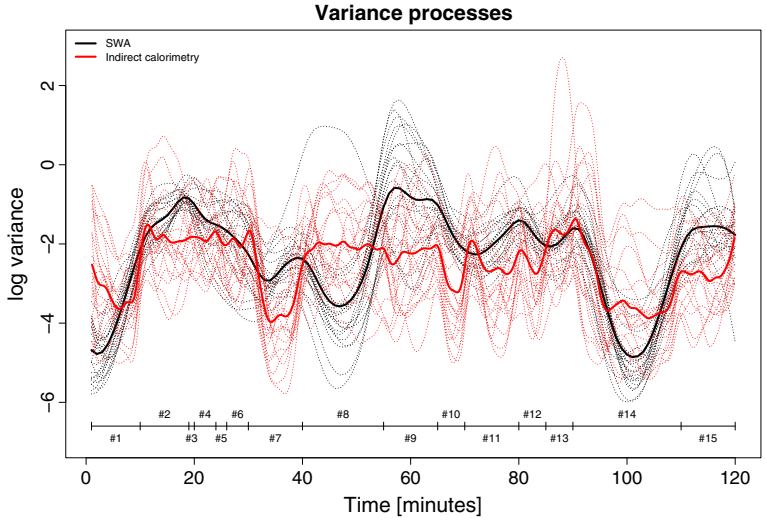

Figure 2 Functional variance processes of the Sensewear pro3 (SWA) and indirect calorimetry measurements showing the internal stability. Lower values indicate higher internal stability. Coding #1-#15 represents intervals of steady state activity (see Table 2).

during horizontal walking, which is comparable with the current observations in hip OA patients [28]. In correspondence with observations in healthy adults [34] and the current observations (during stair climb), Machač et al. (2013) also reported underestimation during walking with inclination [28]. The present pronounced overestimation observed in household and garden activities involving upper body movements is likely to rely on the position of the monitor (accelerometer) on the upper arm.

Due to differences in criterion methods there are limitations concerning comparability of studies since the doubly labeled water method used for validation of daily energy expenditure [11,12,30] does not allow for the activity specific validation attended in the current study design. Generally, studies in healthy adults have been performed at higher intensities compared to the current relatively low intensity protocol which may affect the observed validity. Additionally, the protocols differ largely between studies ranging from highly controlled activities (e.g. treadmill walking and RT-exercises) to various degrees of free living or simulated free living protocols. Physiological changes related to ageing has been suggested as a source to discrepancy between studies in elderly and younger adults [24], however the inaccessible inner algorithms deny further analysis of the individual contributions of the various physiological outputs of the SWA unit.

Clinical implications

The present findings raise concerns regarding the validity in patients with osteoarthritis of the hip, which is important for the application and interpretation of activity monitor estimates within the present patient group, as well as in comparison between patients and healthy subjects. Despite reported high correlation between the SWA and indirect calorimetry the large bias (overestimation) observed during a variety of common activities of daily living represents a major concern for the validity in patients with hip OA. Furthermore, since both bias and variance showed dependency of the type of activity performed, alteration in activities of daily living, as might be expected following surgery or non-surgical interventions may further compromise the validity in clinical use.

Study limitations

The relative low number of participants limits further subgroup analysis. The number of activities in the protocol is restricted which limits generalization of results regarding actual free living. As the overall intensity in the protocol was rather low and the protocol dictated a number of resting periods in between the activities, the bias of a possible carry-over effect (the physiological delay in obtaining steady state after a change in activity) was assumable low, supported by the observed stable bias during the long resting periods (#1, #7 and #14) placed at the beginning, middle and end of the protocol (Figure 1). The intensity of the activities in the protocol makes the results applicable only to a sedentary lifestyle. However, since none of the participants complied to the highest intensity activity (jogging/running) we believe, the protocol reflected typical activities of daily living for the present patient group and a higher intensity protocol was redundant. The use of a walking aid may affect the outcome of activity monitors during walking activities and the exclusion of patients dependent on walking aid limits the generalization of the result regarding hip OA patients with severe functional impairments. Finally, it is a limitation that the outputs from the various sensors of the SWA are inaccessible for analysis regarding their individual contribution to the outcome and their contribution to the error of measurements since the monitor essentially is a “black box”.

Conclusion

In patients with hip osteoarthritis the SWA activity monitor showed substantial bias (overestimation) during common activities of daily living, especially when involving the upper body. Despite a high correlation between the activity monitor and indirect calorimetry, the size and direction of bias and variance between methods varied between activities indicating limited validity of the estimations of physical activity in patients with hip osteoarthritis.

In perspectives, for future prospective studies in patients with hip OA (i.e. in cohort or interventional studies), further validation studies of activity monitors and accelometers are needed as this study emphasizes the importance of both patient and apparatus specific validation studies prior to a clinical application.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

AH: Conception and design, collection of data, analysis and interpretation of the data, drafting of the article, obtaining of funding. MR-L: Conception and design, analysis and interpretation of the data, technical and logistic support. AKJ: Analysis and interpretation of the data, statistical expertise, drafting the article. RH: Analysis and interpretation of the data, statistical expertise. LBA: Conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content. SO: Conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content. AH-L: Conception and design, analysis and interpretation of the data, drafting the article, Critical revision of the article for important intellectual content. All authors read and approved the final manuscript.

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Declaration of contributions
All authors have made substantial contributions to all three of the sections below:
(1) Conception and design of the study or acquisition of data, or analysis and interpretation of data.
(2) Drafting the article or revising it critically for important intellectual content.
(3) Final approval of the version to be submitted.

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Paper 2

Preoperative progressive explosive-type resistance training is feasible and effective in patients with hip osteoarthritis scheduled for total hip arthroplasty - a randomized controlled trial

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Keywords: Strength training, osteoarthrosis, HOOS, muscle power, patient reported outcomes, rehabilitation, total joint replacement

Abstract: To investigate the feasibility and efficacy of progressive explosive-type resistance training (RT) in patients with osteoarthritis (OA) of the hip scheduled for total hip arthroplasty (THA).

Design: Randomized controlled trial (1:1). Eighty patients (age 70.4 ± 7.6 years, BMI 27.8±4.6, 52 females (65%) diagnosed with hip OA and scheduled for THA. The intervention group (IG) performed supervised progressive explosive-type RT twice a week for 10 weeks; four exercises (hip/thigh) performed in 3 series each (8-12 repetition maximum). The control group (CG) received 'care as usual'.

Methods*: Feasibility;* according to adherence, exercise pain (VAS-score) and adverse events. *Efficacy;* according to changes in the 'function' subscale of the Hip Osteoarthritis Outcome Score (HOOS) (primary outcome) and HOOS subscales (pain, symptoms, sport/recreation, and hip related quality of life), leg muscle power (secondary outcomes) were analyzed as intention-to-treat. ClinicalTrials.gov registration: NCT01164111. Results at 12 months post-surgery (primary endpoint) will be reported separately.

Results: Adherence was high (93%) with acceptable exercise related pain (VAS score < 5) reported in 83% of sessions and no adverse events. Changes in HOOS 'function' was 9.7 points 95%CI [4.3; 15.2]

higher in IG compared to CG ($p=0.001$). For all the remaining HOOS subscales IG scored significantly better ($p<0.03$) and had higher leg extension muscle power ($p<0.0001$) compared to CG.

Conclusion: Progressive explosive-type RT was feasible in hip OA patients and resulted in significantly improve self-reported outcomes and increased leg muscle power. This holds promise for better post-operative outcome and rehabilitation.

Introduction:

Osteoarthritis (OA) of the hip is associated with pain, loss of function and impaired leg muscle function [1–6]. Despite functional improvements following surgical treatment with total hip arthroplasty (THA), sustained loss of muscle strength and physical function are reported after surgery[4,7,8]. Low self reported physical function and impaired muscle strength prior to surgery have been reported predictors for poor physical function after THA [9,10]. Thus, enhancing the physical function and improving muscle strength in the late preoperative phase may be of importance for the post operative outcome [11,12].

Preoperative exercise therapy generally has failed to improve muscle function, presumably caused by insufficient conditioning of leg muscle strength despite of medium size effect on improvements in self-reported physical function and pain[13].

Explosive-type resistance training (RT) in patients with hip OA may be of importance for the physical function as leg muscle power (muscle force exerted with speed) is correlated with functional performance in healthy elderly [14,15]. Explosive-type RT as a postoperative intervention appears promising as it has shown to be a feasible and effective way to optimize leg muscle power/strength and physical functioning in healthy elderly [16–19] and in hip OA patients after surgery[5,20–22]. To our knowledge, progressive explosive-type RT has not been investigated as a preoperative intervention in patients with hip OA.

Although pain may be of importance for the efficacy and feasibility of training interventions in hip OA, exercise related pain is inconsistently reported. Ageberg et al, 2010 describe the feasibility of preoperative neuromuscular exercise in hip and knee OA prior to total joint replacement, with low levels of exercise

related pain; however as strenuous RT was not included in this intervention it remains unclear whether explosive-type RT is feasible in patients with symptomatic hip OA[23].

Since no previous studies have reported on preoperative progressive explosive-type RT in hip OA patients, the question was, if such an intervention was feasible and effective in a patient group with symptomatic hip OA. Thus, the purpose of the present paper was twofold; i) to investigate the feasibility of a preoperative progressive explosive-type RT exercise program in hip OA patients scheduled for THA in terms of adherence, exercise related pain, drop-outs and adverse events and ii) to evaluate the efficacy of the intervention on self-evaluated ADL function, as primary outcome and self-evaluated pain/symptoms/sports and recreational function and hip related quality of life in addition to leg extension power as secondary outcomes compared to care-as-usual.

It was hypothesized that a preoperative intervention program with progressive explosive-type RT of medium to high intensity (~70-80% of one repetition maximum) for a duration of 10 weeks with two weekly training sessions was feasible in hip OA patients scheduled for THA and efficient with regard to improve their preoperative physical functioning and muscle function.

Methods:

Study design.

The study was designed as a prospective, randomized (balanced 1:1) clinical trial following the CONSORT guidelines[24]. It was approved by the by the Ethical Committee (Region of Copenhagen, identifier: H-4-2010-034) and conducted in accordance with the Helsinki Declaration II. The study was

registered in ClinicalTrials.gov (identifier: NCT01164111) with primary endpoint 12 months post-surgery. Post-operative results will be reported separately as this article solely reports on the feasibility and efficacy of 10 weeks of explosive-type RT in hip OA patients scheduled for THA prior to surgery.

Eligible participants were: All patients diagnosed with primary hip OA aged 50 years or older, scheduled for THA at the Department of Orthopaedic Surgery, Herlev University Hospital, Copenhagen, Denmark.

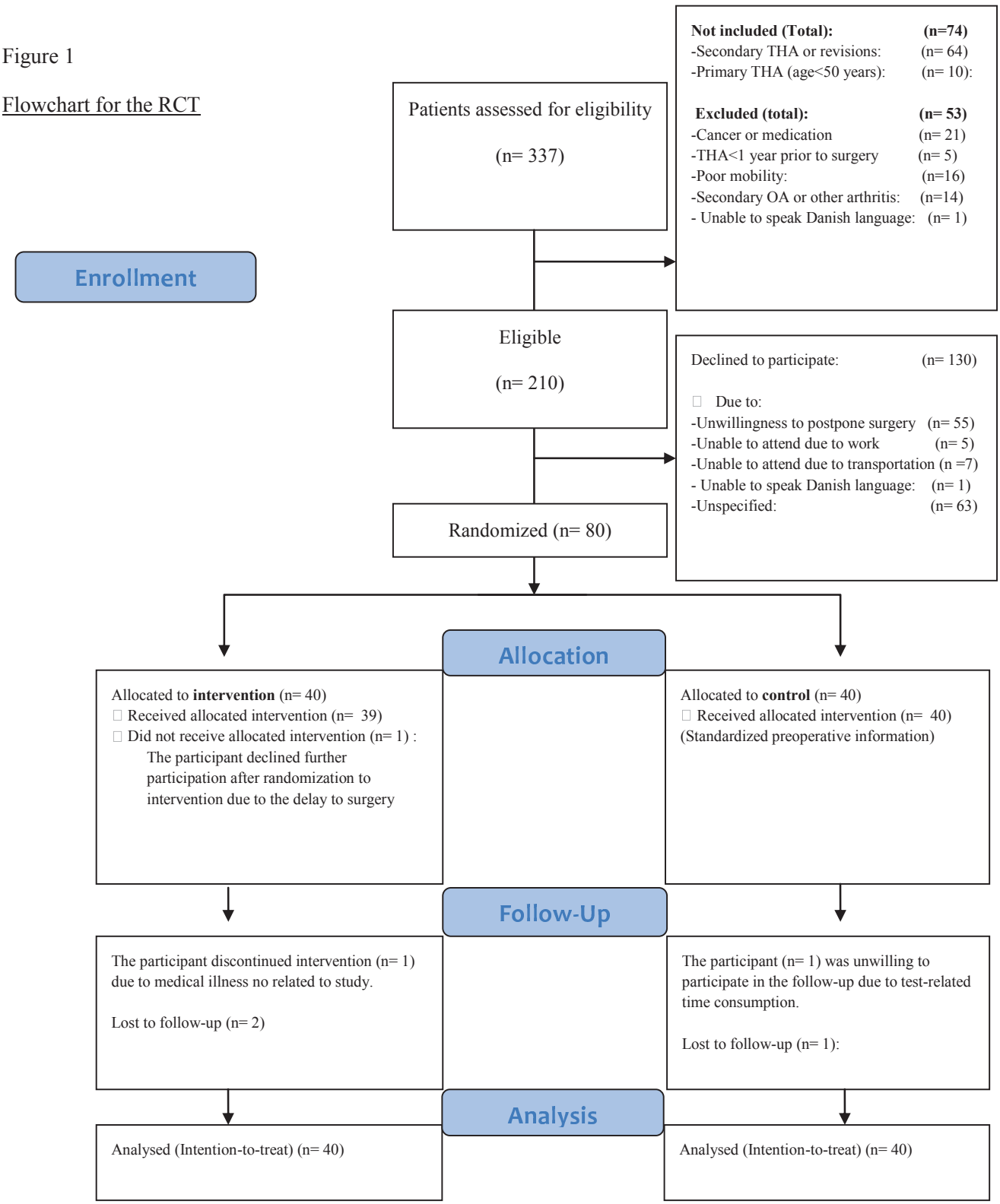
Participants

Exclusion criteria were: Rheumatoid arthritis and other types of arthritis not diagnosed as OA, uraemia, cancer, treatment with systemic glucocorticoids > 3 months the last 5 years with a dose ≥ 5 mg, present or previous hip fracture (either side), other lower extremity fracture within one year prior to inclusion, body weight > 135 kg, severe walking deficits (dependency of two crutches or walker for mobilization), or not speaking Danish language.

The inclusion took place in the outpatient clinic of the Department of Orthopaedic Surgery, Herlev University Hospital, Copenhagen, Denmark. Patients were diagnosed and scheduled for surgery by the hip surgeons. All primary hip OA patients scheduled for THA were registered and subsequently contacted by the principal author for eligibility. Study-information was given in oral and written form. All participants gave informed written consent.

Figure 1

Flowchart for the RCT



Randomisation

Allocation was conducted by the principal author after baseline assessment using sequences of opaque sealed envelopes. A computer generated randomization sequence was used and sequentially numbered closed envelopes containing allocation was produced by a person not otherwise affiliated with the study and concealed from the person enrolling the patients.

The intervention group

The intervention group attended a supervised preoperative progressive explosive-type RT program twice a week for 10 weeks at the Department of Physiotherapy, Herlev University Hospital, Copenhagen, Denmark. The program was initially tested in a pilot group which necessitated minor adjustments according to seating positions and exclusion criteria as severe walking deficits were not compatible with group exercises. Each session lasted one hour and included 10 minutes of warm-up on a stationary bike followed by four exercises on training machines (hip extension, knee extension, knee flexion and leg press) on each leg separately. Exercises were performed in 3 series of 8-12 repetitions. The participants were instructed to complete the concentric phase of the movement 'as fast as possible' according to the principles of explosive-type RT , then pause briefly, and complete the eccentric phase of the movement in approximately 2–3 seconds [25]. The participants were encouraged to perform the maximum number of repetitions possible in each series. If the number of repetitions was below 8 or

exceeded 12, the loading was adjusted for the next series. The individual progression for each participant was monitored by experienced physiotherapists. The participants were teamed up with the same training partner throughout the entire intervention period in order to improve adherence. Training groups were kept small with an upper limit of 8 patients supervised by two physiotherapists. Similar to the control group, the intervention group received the standardized preoperative information by the hip surgeon and attended a 4 hour information meeting at the Department of Orthopaedic Surgery held by nurses and physiotherapists. Surgery was scheduled at 5-7 days after completion of the training intervention.

The control group

The control group received 'care as usual', which besides the standardized pre-operative information by the hip surgeon, included a 4 hour information meeting at the Department of Orthopaedic Surgery held by nurses and physiotherapists and a handout suggesting low-intensity home-based training program without specific RT exercises. The time between inclusion and surgery in the control group reflected actual time-to-surgery which was 1 month according to the treatment guarantee in the Danish Public Healthcare System. There were no restrictions in engaging exercise programs outside the study.

Table 1

Subject characteristics at baseline. Data are x±SD.

	All patients (n=80)	Control (n=40)	Intervention (n=40)
Female gender (N)	52	25	27
Age (years)	70.4 ± 7.6	70.8 ± 7.5	70.0 ± 7.7
Weight (kg)	77.4 ± 15.0	76.5 ± 13.5	78.3 ± 16.5
Height (m)	167 ± 9	167 ± 10	167 ± 9
BMI (kg/m^2)	27.8 ± 4.6	27.4 ± 3.8	28.2 ± 5.3

Outcome measures:

Feasibility and compliance:

The musculoskeletal pain before and immediately after exercise was registered at each training session and the delayed onset of muscle soreness the following day was registered when the patient attended the next training session. Pain was assessed using a continuous visual analog scale (VAS) with 0 being no pain and 10 worst imaginable pains. According to previous exercise studies in patients with musculoskeletal pain[23,26,27] pre-defined cut-off points for "acceptable" pain were used; 'safe';VAS≤2 , acceptable; 2<VAS≤5 and 'high risk'; VAS>5. Participants were informed that delayed onset of muscle soreness after training was expected. However, pain the day after training should not exceed the individual 'normal' pain level for the participant. If scores exceeded these limits the training intensity was decreased on the following session. Drop-outs and adverse events defined as medical illness, musculoskeletal injury or cancelled sessions due to pain and/or injury were registered. Adherence to training was registered from the participants training protocols in terms of number of sessions attended versus number of planned sessions according to protocol in per cent . Good compliance was *a priori* defined as an individual attendance to training of 80% or higher corresponding to 8 weeks of full training.

Efficacy:

Outcome measures were collected at: 1) Baseline (T0) and 2) at preoperative follow-up (T1) after intervention (1-7 days before surgery).

Primary outcome

The 'ADL function' subscale of the Hip disability and Osteoarthritis Outcome Score (HOOS) [28] was selected as primary outcome. HOOS is a patient reported questionnaire of 5 subscales reporting on ADL function, other symptoms, pain, sport & recreation, and hip related quality of life and includes WOMAC (Western Ontario McMaster osteoarthritis score) Osteoarthritis Index LK 3.0 [29]. HOOS has good reliability in hip OA patients (intraclass correlation coefficient (ICC)>0.78) [30] and construct validity and responsiveness is tested[28,31].

Secondary outcomes

Patient reported outcomes

The HOOS subscales 'Other symptoms', 'Pain', 'Sports & Recreation function' and 'Hip related Quality of Life' were selected as secondary outcomes.

Muscle power

Leg extension muscle power (Watt) was measured by the Nottingham Power rig (Nottingham University, Nottingham, UK) and adjusted for bodyweight[32]. Muscle power outcomes were tested and reported with regard to agreement and reliability in a test-retest study with13 hip OA patients

scheduled for THA, meeting identical inclusion and exclusion criteria as the intervention study[33]. Participants were measured twice with 7-10 days between measurements. The within-subject coefficient of variation ($CV_{within\text{-}subjects}$) was used as a measure of agreement to describe the standard error of the measurement. Reliability was expressed by the intraclass correlation coefficient (ICC). Good agreement ($CV_{within\text{-}subjects}$ = 6.3%) and excellent reliability (ICC = 0.97) was observed on unaffected leg whilst moderate agreement ($CV_{within\text{-}subjects}$ = 15.7%) and good reliability (ICC=0.84) was observed on the affected leg.

Procedure for data collection: The initial seating position was registered and maintained for the following tests. Standardized instructions and strong verbal encouragement to perform the most powerful attempt possible were given by the assessor. Both legs were tested separately and trials were continued until no further increase in leg extension power was observed. Best attempt from each leg was used for statistical analysis.

Sample size:

Based upon other clinical studies using HOOS as primary outcome [27] a 'clinical relevant change' was defined as 10 points on the HOOS 'function' sub scale. In order to identify such a difference the calculated group size was n= 35 given a power of 0.80, $\alpha = 0.05$, and SD = 15). A group size of 40 for each group was chosen to compensate for loss to follow-up.

Statistics:

Agreement and reliability of leg extension muscle power:

$CV_{within\text{-}subjects} = \frac{SD}{\overline{X}}$ x 100, where $\overline{X} = \frac{\overline{X}\,test - \overline{X}\,retest}{2}$

and SD= $\sqrt{\frac{(d^2)}{2n}}$, where *d*= test – retest and *n* = number of participants

ICC was interpreted as the proportion of the total residual variance that is due to the residual variability between subjects:

$$\frac{\sigma_\alpha^2}{\sigma_\alpha^2 + \sigma_\epsilon^2}.$$

The calculation of ICC was based on one-way analysis of variance.

Efficacy:

Outcomes at baseline and follow-up were reported in mean (SD). The primary analysis was intended-to-treat and involved all patients randomly assigned. There was no difference between intention-to-treat and per-protocol analysis. The last observation was carried forward in cases where data were missing. Adjusted between group differences mean (95%CI) was analyzed by a multilevel regression model adjusting for baseline, group, sex, age and BMI. The model was checked for homogeneity of residuals and normality. A two-sided p-value of 0.05 was set as significance level providing evidence against the null hypothesis. Effect size in terms of the standardized mean difference including 95% CI was reported as Cohen's *d* using pooled SD and indexes for small, medium and large effects as proposed by Cohen, 1992[34]. Software used for statistical analysis: STATA 11.1, StataCorp, Texas, USA.

Results:

Eligible participants were recruited from April 2011 to June 2012 (CONSORT flowchart; see Figure 1). The 80 patients eventually being randomized were aged 70.4 ± 7.6 years at baseline and 65% (n=52) were female (baseline characteristics; see Table 1). Three patients were lost to follow-up: One patient (control) dropped out after baseline due to unwillingness to further testing and one patient (intervention) dropped out between baseline and start up of intervention due to the delay of surgery in the intervention group compared to care-as-usual. One patient (intervention) was excluded from the study after 2 weeks of intervention due to medical illness not related to the study (pneumonia). There were no differences between groups regarding any of the patient's characteristics. Thirty eight patients (95%) completed the 10 weeks of intervention. The 130 eligible patients unwilling to participate were on average 70.5±8.2 years old and 58 % were female. The primary reason to decline participation (42%) was delay of surgery beyond the 1 month treatment guarantee.

Mean time between baseline and follow-up was 10.5 weeks for the intervention group and 3.5 weeks for the control group.

Table 2

The efficacy of 10 weeks of preoperative explosive-type RT on patient reported outcomes (HOOS). Between-group difference at preoperative follow-up is adjusted for baseline, sex, age and BMI.

	Intervention Group		Control Group		
Outcomes	Baseline	Follow-up	Baseline	Follow-up	Adjusted between-group difference at follow-up*
Primary Outcome HOOS					
ADL function	49.2(12.5)	58.9(17.3)	48.1(13.8)	48.3(13.9)	9.7(4.3 to 15.2)
Secondary Outcomes HOOS					
Pain	48.0(12.7)	55.4(16.9)	46.3(14.4)	45.9(14.1)	8.2(2.1 to 14.3)
Symptoms	44.5(16.4)	55.9(19.6)	43.1(18.5)	45.3(16.7)	10.3(4.0 to 16.5)
Sports & Recreation	28.1(15.2)	37.8(18.7)	27.8(17.7)	28.3(15.4)	9.9(3.4 to 16.4)
Hip related QOL	32.1(14.4)	38.6(17.1)	29.2(15.6)	30.5(14.3)	6.2(0.5 to 11.8)
Secondary Outcomes Leg extension power					
Affected side (Watt/Kg)	1.5(0.6)	1.9(0.7)	1.4(0.7)	1.4(0.7)	0.4(0.2 to 0.5)
Unaffected side (Watt/Kg)	1.9(0.7)	2.2(0.8)	1.8(0.8)	1.7(0.8)	0.4(0.2 to 0.5)

*) Adjusted for baseline, sex, age and BMI.

Outcomes:

Feasibility of intervention

For patients completing the intervention (n=38) the average adherence to sessions was 93 % and all patients completed with an attendance ≥ 80%. VAS ≤5 immediately after training was reported in 95% of the sessions while VAS≤5 within training day and the following day was reported in 83% of the sessions. Immediate exercise related musculoskeletal pain (VAS>5 immediately after training) was reported in 9% of the early sessions (week 1+2) and in 1% of later sessions (week 9+10). VAS>5 one day after training was reported in 34% of the early sessions (week 1+2) and 6% of the later sessions (week 9+10). An exercise session was skipped due to pain on two occasions by one patient. No patients withdrew from the intervention group due to pain or musculoskeletal injury. One patient reported temporary swelling and pain of the knee joint.

Efficacy of intervention

Primary outcome:

For HOOS, ADL the intervention group scored 9.7 points 95%CI [4.3; 15.2] higher compared to controls at follow-up (p=0.001) (Table 2) with an effect size of 0.8 (Table 3).

Secondary outcomes:

All remaining HOOS sub scales ('pain', 'symptoms', sports and recreational function, hip related quality of life') showed significant improvement in the intervention group (p-value< 0.03) (Table 2) with effect

sizes between 0.4 and 0.6 (Table 3).

Leg extension power: For both the affected and unaffected leg the leg extension power was significantly higher in the intervention group compared to controls ($p<0.0001$) with a similar between group difference at follow-up for both legs; 0.4Watt/Kg 95%CI [0.2 to 0.5] (Table 2). Effect sizes were 0.5 (unaffected leg) and 0.6 (affected leg) (Table 3).

Table 3

Effect size on primary and secondary outcomes expressed by Cohen's D

Outcomes	**Pooled SD**	**Cohen's D (95% CI)**
Primary Outcome HOOS		
ADL function	13.0	0.8(0.3 to 1.2)
Secondary Outcomes HOOS		
Pain	13.4	0.6(0.2 to 1.1)
Symptoms	17.2	0.6(0.2 to 1.1)
Sports & Recreation	16.3	0.6(0.2 to 1.1)
Hip related QOL	14.8	0.4(0.0 to 0.9)
Secondary Outcomes Leg extension power		
Affected side (Watt/Kg)	0.64	0.6(0.2 to 1.1)
Unaffected side (Watt/Kg)	0.74	0.5(0.1 to 1.0)

Discussion:

In this RCT we report the feasibility and efficacy of 10 weeks of progressive individualized explosive-type RT compared to 'care as usual' in patients with primary hip OA scheduled for THA. Explosive-type RT is a promising preoperative intervention since it has proven its efficacy for improvement of important elements of physical functioning and muscle function in healthy elderly[16–19] and in hip OA patients after THA[21] . To our knowledge, this study is the first to report on preoperative progressive explosive-type RT in symptomatic hip OA patients scheduled for THA.

The intervention demonstrated to be feasible in hip OA patients scheduled for THA in terms of high adherence to training and low levels of exercise related pain. No serious adverse events or drop-outs were reported for exercise related reasons.

The study showed significant improvements in favour of intervention for all 5 patient reported HOOS subscales, including self-reported ADL function (primary outcome) supported by significant higher leg muscle power compared to controls.

Feasibility of preoperative progressive explosive-type RT in hip OA patients

Intervention was well accepted with high adherence to training, no drop-outs related to intervention, and no serious exercise related adverse events. Good compliance (*a priori* defined adherence ≥ 80% of the sessions) was achieved by all participants completing training (n=38). These observations are similar to adherence rates in previous studies of preoperative exercise therapy [35–38]. According to feasibility in terms of exercise related pain, acceptable pain levels immediately after training (VAS≤5) were reported in 95% of all sessions with low prevalence of VAS>5 throughout the intervention. As expected for a group of untrained individuals, the intervention group reported exercise induced delayed onset of muscle soreness

defined as VAS> 5 the day after training. Although VAS >5 the day after training was reported in approximately 1/3 of the sessions during the initial 2 weeks of the exercise program, acceptable pain (VAS≤5) within the training day and the following day was reported in 83% of all sessions. Feasibility according to exercise related pain is not commonly described in relation to preoperative exercise in hip OA patients. For neuromuscular exercises (including low intensity RT as a adjunct) Ageberg et al 2010 reported similar levels of acceptable immediately post exercise pain (93.8 % of the sessions) during a preoperative intervention in patients with OA of the hip and knee, indicating medium to high intensity explosive-type RT to be equally feasible, although delayed onset muscle soreness was not reported[23].

Efficacy of preoperative exercise therapy in hip OA patients

Preoperative exercise therapy in patients scheduled for THA have previously been investigated with interventions ranging from home based to hospital based exercise programs[13,35–41] but the efficacy of isolated progressive explosive-type RT have not been investigated.

Few studies have included various types of 'strengthening exercises' as an adjunct to aerobic exercises[35,37–39,41].Opposed to the present findings, all studies except one (Gilbey et al 2003) reported no significant change muscle function prior to surgery[35]. This indicates that previous exercise interventions may not have provided sufficient loading and/or progression of the strengthening exercises to improve muscle function outcomes since only one previous study qualify for the content of progressive RT[4213]. Gilbey et al, 2003 reported that 8 weeks of slow velocity progressive RT (applied both before and after surgery) increased a combined leg strength score in the intervention group with a significant difference at preoperative follow-up (p= 0.04). However, the size of the effect (e.g. the between group difference at

follow-up) was not reported and since the intervention group received RT both before and after surgery it was not possible to determine the postoperative effect of the preoperative part of the intervention[35,39].

The patient's perspective is of primary interest in the evaluation of interventions in OA and thus a validated patient reported outcome is generally recommended as primary outcome[43]. In four of the studies with strengthening exercise as an adjunct, 'function' was evaluated with validated patient reported outcomes (HOOS or WOMAC)[35,37,38,41] but only two studies[35,38] observed a significant effect on function in favour of exercise indicating only limited value for ADL improvement.

A meta-analysis of preoperative interventions including both strengthening, flexibility, and/or aerobic activities in hip and knee replacement surgery reported medium size effect on self reported pain and function[13]. A recent RCT (published later) evaluating preoperative neuromuscular training (without progressive RT) reported a medium effect size regarding both ADL function and pain in hip OA patients prior to THA; however the effects was not sustained 3 month after surgery[27,44]. Regarding muscle function,Villadsen et al (2014) found no significant effect on single joint muscle power or leg extension power at preoperative follow-up[44]. However, a significant between group difference regarding single joint muscle power (hip abduction/extension) but difference in leg extension power was reported at 3 months follow-up after surgery [27]. In comparison, the present study show a large size effect on self-evaluated ADL function (Cohen's *d*; 0.8) and medium size effect (Cohen's *d*; 0.5-0.6) on pain and muscle function (leg extension power) following 10 weeks of explosive-type RT. Heterogeneity concerning the outcome measures is a major restriction for comparison of studies and only one previous study combines self-reported outcomes with muscle function outcomes [38]. Conclusions concerning possible effects of previous intervention studies are further compromised by small sample sizes and unclear definitions of key aspects of the interventions (intensity, training volume, dose, duration, and progression)[45]. As the duration

of the intervention is an aspect of the total amount of exercise it may also be of importance that all previous studies have shorter interventions (3 to 8 weeks) compared to the present 10 weeks. Our results might be explained by the systematic and progressive setting of isolated RT over 10 weeks in small groups assisted by dedicated physiotherapist, as dose and progression of previous interventions may not comply with the general recommendations regarding RT exercise [46].

Clinical implications

Our findings indicate that progressive explosive-type RT is feasible in patients with hip OA scheduled for THA and significantly increases self reported ADL function by 9.7 points compared with CG (p=0.001), which is slightly lower than the 10 points *a priori* defined as being a 'clinically relevant' difference[27]. However, there is no consensus cut-point to define a clinically relevant difference for HOOS outcomes in hip OA patients prior to THA. Tubach et al (2005) reported a change of 7.9 on the WOMAC 'function' as 'minimal clinical important improvement' in hip OA patients in medical treatment not scheduled for surgery[47]. Since the subscale 'ADL function' within HOOS and WOMAC is identical, the present between group-difference of 9.7 points may represent a clinically relevant effect. For patients with less severe symptoms, an absolute improvement in function of 9.7 points may even become relevant for postponing or cancelling surgery[47]. Although not an issue in the present study, it will be attended in a future study[48]. Establishing cut points for minimal clinical change (MCII) for patient reported outcomes have been attempted in relation to the surgical intervention (THA) were indices of improvements between 38% and 55% were needed[49]. However, the MCII for a surgical

procedure may not be readily comparable with interventions based on exercise considering the large differences in cost and risks.

Leg muscle function in terms of muscle power is highly correlated with physical functioning in elderly[14,15]. The current improvements in leg muscle power are comparable with similar interventions in healthy elderly without OA[18,19] indicating progressive explosive-type RT to be a effective intervention for improving muscle function even in symptomatic hip OA patients. The present observed improvements in both self-reported function and muscle function prior to surgery may have a clinically relevant effect on post-surgical rehabilitation as low pre-operative patient-reported function and muscle strength is associated with poor functional outcome after THA[9,10]. One recent high quality randomized clinical trial of preoperative neuromuscular exercise (without medium to high intensity RT), reported significant post-operative effects on early-phase (+ 6 weeks) self-evaluated physical function and pain but no sustained effects 3 months after hip or knee arthroplasty[27].

Limitations

The external validity of the present study might be harmed by the number of eligible non participants. The exclusion of patients with severe needs for walking assistance, hinder the implications in patients with major mobility deficits. Also patients employed in day time jobs may find it difficult to participate in sessions within normal working hours. However, only a minor number of patients reported problems attending their jobs as the major cause for declining participation.

The shorter time of up to 6 weeks to surgery in the control group may hamper the internal validity. On the other hand this has strengthened the external validity as this would happen in the daily clinic. In addition, a recent meta-analysis provides strong evidence that self reported pain and function in hip OA patients do not deteriorate during waiting times (< 180 days) to THA [50].

Assessor blinding was not possible to implement without violation, since logistics at the combined test and training site made sufficient masking impossible. To avoid this source of bias, a standardized protocol for instruction and verbal encouragement was followed strictly during the collection of muscle power outcomes. Moreover, the patient reported outcomes (HOOS) which included the primary outcome were not subject to assessor bias

Conclusion

Progressive explosive-type RT is feasible in patients with hip OA scheduled for THA. The intervention significantly improved immediate preoperative self reported outcomes including physical function and pain, hip related quality of life and leg muscle power was increased. The effect sizes of the improvements indicate that progressive explosive-type RT of medium to high intensity twice a week for a period of 10 weeks is an effective intervention for improving ADL, function in hip OA patients prior to THA.

In perspective, the present study holds promise for an accelerated or even improved post-surgery rehabilitation.

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Contributions

All authors have made substantial contributions to all three of the sections below:

(1) Conception and design of the study or acquisition of data, or analysis and interpretation of data.

(2) Drafting the article or revising it critically for important intellectual content.

(3) Final approval of the version to be submitted.

Specifics: AH: Conception and design, collection of data, analysis and interpretation of the data, drafting of the article, obtaining of funding. AHL: Conception and design, interpretation of the data, critical revision of the article for important intellectual content. BZ: Conception and design, interpretation of the data, technical support, critical revision of the article for important intellectual content. SM: Conception and design, interpretation of the data, critical revision of the article for important intellectual content. SO: Conception and design, interpretation of the data, critical revision of the article for important intellectual content. All authors read and approved the final manuscript.

The primary author; Andreas Hermann (ahermann@dadlnet.dk) takes responsibility for the integrity of the work as a whole, from inception to finished article.

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The authors certify that the grant sponsor has no involvement in study design, collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

Competing interests

The authors declare no competing interests

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Paper 3

Changes in muscle strength, physical functioning and body composition following preoperative resistance training – an explorative randomized clinical trial in patients with hip osteoarthritis.

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Abstract:

Aim: To investigate changes in muscle strength, fat free mass and physical functioning following explosive-type resistance training (RT) in patients with osteoarthritis of the hip scheduled for total hip arthroplasty and to identify muscle determinants relevant for improvements in physical function.

Design: Randomized explorative trial (1:1). Eighty patients (age 70.4 ± 7.6 years, BMI 27.8±4.6, 52 females (70%)) diagnosed with hip OA and scheduled for THA. The intervention group (IG) performed supervised progressive explosive RT twice a week for 10 weeks; four exercises (hip/knee) in 3 series (8-12 repetition maximum). The control group (CG) received 'care as usual'.

Method: Between-group changes in leg muscle strength (maximal isometric strength and rate of force development), fat free mass and physical functioning (stair negotiation and horizontal gait) were analyzed as intention-to-treat. Correlation analyses were performed as changes in muscle strength or fat free mass versus changes in physical functioning. ClinicalTrials.gov registration: NCT01164111. Results for primary and secondary outcomes at 12 months post-surgery (primary endpoint) will be reported separately.

Results: In the intervention group muscle strength was significantly higher than the control group at follow-up ($p<0.02$). Intervention group improved physical functioning (8%-20%, $p<0.0001$) and increased regional FFM (2%, $p=0.001$) to a larger extent than the control group. In the intervention group moderate associations ($r=0.30$-0.41, $p<0.012$) were found between changes in isometric knee extension and stair negotiation.

Conclusion: Preoperative explosive-type RT resulted in significantly improved isometric muscle strength, increased FFM and enhanced physical function in hip osteoarthritis patients compared to care-as-usual. Correlation analysis indicated maximal knee extension to be an important determinant for stair negotiation.

Introduction

Osteoarthritis (OA) of the hip is believed to contribute to impaired muscle strength and muscle atrophy due to disuse of the lower extremity [1–3]. In activities of daily living (ADL), especially those requiring demanding functions, the leg extensor muscles play an important role [4] and accentuated loss of leg muscle strength as observed in hip OA patients may impose a threat to the functional independence[5].

For hip OA patients with progressive pain and impaired function, joint replacement surgery can improve physical functioning. However, a sustained loss of muscle strength relevant for activities of daily living is reported post surgery[1,6,7] and full recovery of physical function to a pre-disease state should not be expected[6].

Theoretically, a preoperative enhancement of functional status may transform to a faster recovery and better postoperative outcome[8]. Various preoperative exercise studies have failed to provide evidence for preoperative effects on muscle strength or objectively measured physical function [9–13]. However, the effects of strenuous explosive-type resistance training (RT) in the preoperative stage remain unclear.

RT performed with maximal intentional velocity of the load during the concentric phase (explosive-type RT) has proven to be effective in improving mechanical muscle capacity and physical functioning in healthy elderly adults[14,15]. Despite these findings, explosive-type RT is yet to be investigated as a preoperative intervention in patients with hip OA scheduled for total hip arthroplasty (THA).

The aims of this explorative RCT were to investigate i) the effect of preoperative explosive-type RT on maximal muscle strength, ii) body composition (fat free mass) and iii) the possible associations between changes in muscle function and changes in physical ADL functions and body composition

We hypothesized that 10 weeks of explosive-type RT could increase physical functioning, maximal isometric muscle strength and explosive strength characteristics plus fat free mass and that these changes associate with improvements in strenuous ADL, such as stair ascending/descending.

Methods

Participants:

Three hundred and thirty seven patients scheduled for hip surgery were assessed for eligibility in the out-patient clinic at the Department of Orthopedic Surgery, Herlev Hospital, Denmark from 1. April 2011 to 1. August 2012, of which 263 were primary hip OA patients > 50 years of age scheduled for THA. Fifty three were excluded due to criteria (see below) leaving 210 eligible of which 80 (52 women) participated in the study (Fig 1 – CONSORT flow chart). One hundred and thirty eligible patients declined to participate mainly due to unwillingness to postpone surgery due to intervention. Criteria for exclusion were; arthritis not diagnosed as OA, uraemia, cancer, treatment with systemic glucocorticoids (> 3 months the last 5 years with a dose ≥ 5 mg/day), present or previous hip fracture, other fracture at the lower extremities within one year prior to inclusion, body weight > 135 kg, severe walking deficits requiring two crutches or walker, or not speaking Danish language.

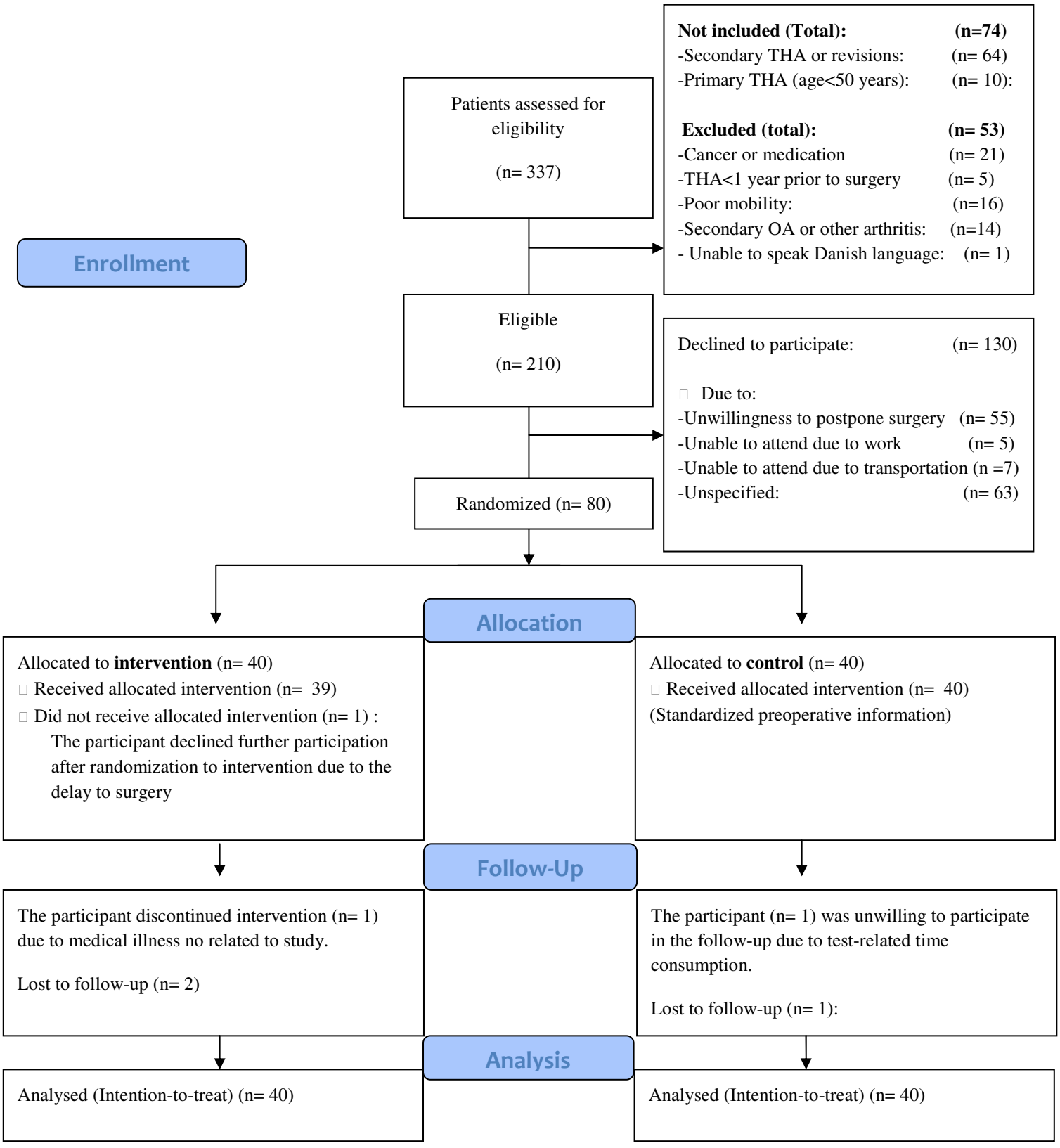
Table 1

Subject characteristics at baseline. Data are $\bar{x}$±SD

	Intervention group (total) (n = 40)	Control group (total) (n = 40)	Intervention group Female (n = 27)	Control group Female (n = 25)	Intervention group Male (n = 13)	Control group Male (n = 15)
Age (years)	70.0 ± 7.7	70.8 ± 7.5	71.7 ± 7.0	73.3 ± 6.8	66.7 ± 8.4	66.8 ± 8.4
Weight (kg)	78.3 ± 16.5	76.5 ± 13.5	73.5 ± 15.5	71.2 ± 12.0	88.2 ± 14.1	85.3 ± 11.3
Height (m)	166.7 ± 9.3	166.8 ± 9.6	162.0 ± 7.0	161.5 ± 6.1	175.9 ± 5.9	175.7 ± 7.4
BMI (kg/m^2)	28.2 ± 5.3	27.4 ± 3.8	28.0 ± 5.3	27.3 ± 4.1	28.5 ± 4.6	27.7 ± 3.3

Figure 1

Flowchart



This explorative study was based on the cohort of a prospective, randomized (balanced 1:1) clinical trial (RCT) registered in ClinicalTrials.gov (identifier: NCT01164111) with primary endpoint 12 months post-surgery. Sample size of the cohort was based on a power calculation regarding the primary outcome for the RCT; the subscale 'Function' of the Hip Dysfunction and Osteoarthritis Outcome Score (HOOS) which will be reported elsewhere. The present explorative study reports only on preoperative changes in explorative outcomes (leg muscle strength, body composition, and physical functioning). Feasibility and patient-reported efficacy as well as postoperative outcomes will be reported separately. The study was approved by the by the Ethical Committee (Region of Copenhagen, identifier: H-4-2010-034) and performed in accordance with the Helsinki Declaration II.

The 80 participants were allocated into an intervention group (n= 40) and a control group (n=40) by a third person otherwise not related with the study using concealed computer generated randomization. Sufficient masking to obtain effective assessor blinding was not possible due to the logistic setup. However, a protocol ensuring standardization during testing was followed to minimize any bias related to data collection. The intervention group received 10 weeks of preoperative RT (see below) and the control group received care-as-usual which included a voluntary home based exercise program without RT. For participants in the control group surgery was scheduled according to the regular waiting list, which was 1 month according to the treatment guarantee in the Danish public health care system.

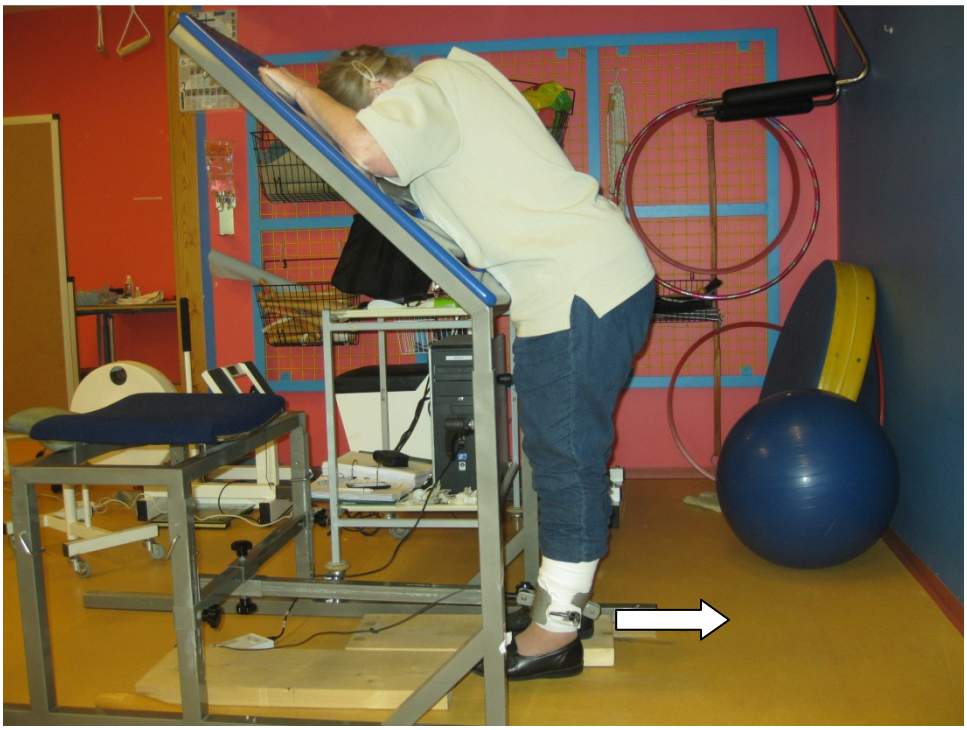
Outcomes were collected at two occasions prior to surgery; 1) Baseline measurement after enrollment and 2) follow-up after intervention (2-5 days before surgery). Before testing the participants performed 5 minutes of warm-up on stationary exercise bike.

Isometric muscle strength:

Single-joint isometric muscle strength was measured as maximal voluntary contraction (MVC) during unilateral knee extension and hip extension in a custom build test chair based upon conventional strain-gauge technique (Fig 2). A rigid metal clamp system was attached 2 cm above the malleoli and horizontally connected to a strain gauge fixed to the construction. To calculate *isometric muscle torque* (force x lever arm (Nm)) the vertical distance between center of the metal clamp and the joint axis was measured by a ruler. Knee extension was measured in seated position with the knee joint in 90 degrees flexion while hip extension was measured in standing position with 45 degrees hip flexion and ground support from the contra-lateral leg. This forward position during hip extension was chosen according to relevance in core activities of daily living like stair climb, walking and chair rise[1]. A standardized instruction was used including verbal encouragement to perform the strongest and most explosive attempt possible and on-line visual feedback to the participant on a computer screen was provided. Multiple trials (contractions of approximately 4 seconds followed by 30 second pauses) were provided for each leg separately, until no further improvement was observed in MVC. The trial with highest MVC was selected for further analysis and normalized for body weight. Contractile rate of force development (RFD) was calculated as the mean tangential slope of the selected force-time (Δforce/Δtime) curve in the initial 200 ms of the contraction and normalized for body weight. RFD was chosen, as the ability to rapidly increase force during the initial phase of muscle contractions is of importance in many aspects of ADL including reversing falls[15–17].

Figure 2

Isometric knee /hip extension test.



Stair negotiation:

Stair negotiation[18] was performed at self-selected maximal speed while ascending and descending 10 steps (step height; 15cm) from standing position until the last step was reached with both feet. Use of rails was allowed only if needed for a safe execution. Ascending and descending was timed separately and performed twice. Fastest time (steps per second) for each outcome was used.

Gait speed (20 meters):

Timed 20 meters walk[19] from a standing position (normal and maximal walking speed)[19]. A walking aid was allowed if needed for safe execution. Each test was performed twice. Fastest maximal walking speed (meters per second) and the average speed of the two normal walking speed tests were used.

Timed sit-to-stand test (5 repetitions). The patient was seated in a standardized straight-backed chair with arm rests (seat height 45 cm)and instructed to perform 5 times repeated stand up/sit down as fast as possible with arms folded across the chest. The patient was timed from the initial sitting position to the final standing position after 5 repetitions. For familiarization the patient performed a single sit-to-stand prior to each test.

Body composition:

A full body mini fan beam dual-energy X-ray absorptiometry (DXA) scans was used (Lunar Prodigy scanner (GE Lunar, Madison WI, USA)) for measuring of fat mass (FM) and fat free mass

(FFM). One scanner (serial nr. DF+13189) was used for all participants utilizing software version 14,10,022. Daily quality assurance was performed using the standard phantom supplied by the manufacturer and additional control scans were performed with a spine phantom (Hologic: Anthropomorphic spine phantom, model DPA/QDR-1, serial no.(S/N): 71010) three times weekly. DXA has been validated against computer tomography (CT) and magnetic resonance (MR) as golden standards in elderly and fat free mass as an estimate for muscle mass was found reliable and valid[20–22]. For analysis of regional changes in fat free mass, the femoral region was selected *a priori* as area of interest according to the muscle groups targeted by the intervention (knee extensors/flexors, hamstring and hip extensors). The area of interest was defined using validated regional landmarks[21,22].; the proximal limit was defined by a horizontal plane through the lowest point of the ischiadic tuberculum and the distal limit was defined by a horizontal plane through the knee joint. Medial and lateral limits for each femoral region were the median plane through the pubic symphysis and the lateral aspect of the body region, respectively.

Test-retest reliability:

Reliability (intraclass correlation coefficient; ICC) and agreement (within subject coefficient of variance; $CV_{within\text{-}subjects}$) of isometric muscle strength measures and functional outcomes were initially tested in a test-retest study with15 hip OA patients scheduled for THA, meeting identical inclusion and exclusion criteria as the current intervention study. Participants were measured twice with 7-10 days between measurements. Good to moderate agreement ($CV_{within\text{-}subjects}$, range = 4.2%-13.5%) and good to excellent reliability (intra-class correlation = 0.82 – 0.97) were observed for 20 meter horizontal walk test and stair negotiation. Knee extension showed moderate agreement ($CV_{within\text{-}subjects}$ = 11.5% and 16.7% for the affected and non-affected leg, separately) and good reliability (ICC =0.90 and 0.70 for the affected)and non-affected, respectively). For hip extension

moderate agreement ($CV_{within\text{-}subjects}$ = 9.5% and 15.6% for the affected and non-affected leg, respectively) and good to excellent reliability (ICC = 0.96 and 0.87 for the affected and non-affected leg, respectively) were observed.

Resistance Training:

A progressive explosive-type resistance training program[14,17,23] was performed twice a week for a period of 10 weeks prior to surgery. The duration of each training session was one hour and included 10 minutes of warm-up on a stationary exercise bike followed by four RT exercises on training machines (hip extension, knee extension, knee flexion and leg press). Exercises were performed unilaterally (each leg separately) and in 3 series of 8-12 repetitions at 8-12 repetition maximum. Participants were instructed to complete the concentric phase of the movement 'as fast as possible', pause briefly, and complete the eccentric phase of the movement in approximately 2–3 seconds [14,17,23] and encouraged to perform the maximum number of repetitions possible in each series. With number of repetitions below 8 or exceeding 12 the loading was adjusted for the next series. The individual progression for each participant, exercise technique, and movement explosiveness were continuously monitored and adjusted by trained physiotherapists at each session.

Statistics:

An intended-to-treat analysis involving all patients randomly assigned was performed. The baseline observation was carried forward in cases where data were missing. Between-group differences at follow-up were analyzed by a multilevel regression model adjusting for baseline, group, gender, age

and BMI. Analysis for associations between pre to post intervention changes in muscle strength characteristics or functional outcomes versus changes in body composition were carried out using simple regression. A two-sided p-value of 0.05 was set as significance level providing evidence against the null hypothesis. Software used for statistical analysis: STATA 11.1, StataCorp, Texas, USA.

Results

Of the 80 patients initially randomized, 3 patients were lost to follow-up (Fig 1). The average adherence to planned training sessions for the intervention group was 93% with individual compliance ranging from 80% to 100%.

At baseline there were no differences between groups according to anthropometric measures (Table 1), muscle strength characteristics, physical function or body composition (Table 2).

Muscle torque: The intervention group had significant stronger maximal knee extension and hip extension torque on both sides compared to the control group at follow-up (Table 2). Explosive muscle characteristics (RFD) for knee and hip extension were significantly higher in the intervention group on the affected side compared to the control group at follow-up, while for the unaffected side only rate of force development for hip extension improved significantly following intervention (Table 2).

Body composition: In the intervention group a significant higher fat free mass (total body and femoral regions) were observed at follow-up (Table 2). There was no difference between the two groups regarding fat mass, bodyweight and BMI.

Table 2

The effect of explosive-type resistance training on muscle strength, physical functioning and fat free mass. Outcomes at baseline and follow-up are $\bar{x}$±SD. Adjusted between-group differences are $\bar{x}$(95% CI).

	Intervention Group		Control Group		
Outcomes	Baseline	Follow-up	Baseline	Follow-up	Adjusted between-group difference at follow-up*
Leg muscle strength					
MVC Knee extension affected side (Nm/Kg)	1.17(0.39)	1.36(0.39)	1.17(0.45)	1.10(0.43)	0.27(0.18 to 0.35)
MVC Knee extension Unaffected side (Nm/kg)	1.30(0.44)	1.50(0.51)	1.29(0.46)	1.20(0.41)	0.31(0.22 to 0.40)
MVC Hip extension Affected side (Nm/Kg)	1.52(0.58)	1.85(0.60)	1.57(0.64)	1.53(0.60)	0.40(0.24 to 0.49)
MVC Hip extension Unaffected side (Nm/kg)	1.61(0.55)	1.97(0.62)	1.62(0.67)	1.61(0.60)	0.40(0.30 to 0.51)
RFD200 Knee extension Affected side (Nm/Kg)	2.72(1.31)	3.16(1.27)	2.79(1.58)	2.66(1.44)	0.59(0.22 to 0.95)
RFD200 Knee extension Unaffected side(Nm/Kg)	3.19(1.56)	3.53(1.58)	3.20(1.85)	3.13(1.59)	0.45(0.01 to 0.90)
RFD200 Hip extension affected side (Nm/Kg)	3.56(2.56)	4.55(2.63)	3.52(3.05)	3.61(2.68)	1.07(0.19 to 1.97)
RFD200 Hip extension unaffected side(Nm/Kg)	3.95(2.32)	4.47(2.03)	3.79(3.39)	3.76(2.95)	0.67(-0.04 to 1.37)
Physical functioning					
Stair climb ascending (steps/sec)	1.7(0.6)	2.0(0.7)	1.8(0.8)	1.8(0.8)	0.4(0.2 to 0.5)
Stair climb descending (steps/sec)	1.9(0.8)	2.3(0.8)	2.0(1.0)	2.0(1.0)	0.4(0.2 to 0.5)
Horizontal gait speed 20 m (normal) (m/sec)	1.2(0.2)	1.3(0.2)	1.2(0.3)	1.2(0.3)	0.1(0.1 to 0.1)
Horizontal gait speed 20 m (max) (m/sec)	1.5(0.3)	1.7(0.4)	1.5(0.4)	1.5(0.4)	0.2(0.2 to 0.3)
Sit to stand x 5 (s)	14.5(5.4)	11.6(4.4)	15.1(6.9)	14.4(6.6)	-2.1(-3.2 to -0.9)
Muscle mass					
Total fat free mass (Kg)	46.7(9.6)	47.1(9.7)	46.3(10.6)	46.1(10.5)	0.6(0.1 to 1.1)
Fat free mass femur affected side (Kg)	4.4(1.1)	4.5(1.2)	4.4(1.2)	4.3(1.2)	0.2(0.1 to 0.3)
Fat free mass femur unaffected side (Kg)	4.5(1.1)	4.59(1.2)	4.51(1.2)	4.47(1.2)	0.1(0.1 to 0.2)

*) Adjusted for baseline, sex, age and BMI.

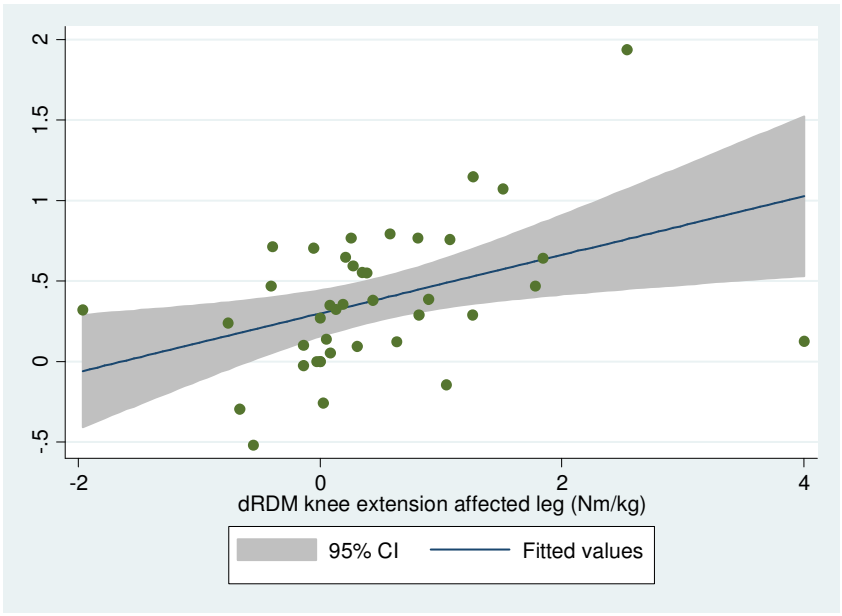
Physical functioning: For all physical function tests (horizontal gait (normal and maximum speed), stair climb and sit-to stand), participants in the intervention group performed significantly faster compared to controls at follow-up (Table 2).

Association analysis: For participants in the intervention group there was a moderate linear relationship in the intervention group between pre-to-post-training changes in ascending and descending stair walk speed versus changes in knee extension MVC of the affected side ($r = 0.34$, $p= 0.029$ and $r = 0.39$, $p= 0.012$, for ascending and descending respectively) (Figure 3). Similarly, change in descending stair walk speed was associated with changes in knee extension RFD ($r = 0.41$, $p = 0.009$ and $r=0.30$, $p=0.005$ for affected and unaffected side, respectively). Within the intervention group no significant associations were found between changes in horizontal speed and changes in MVC (hip or knee) or RFD (hip or knee). Furthermore, no significant associations were found between changes in femoral fat free mass and changes in neither muscle strength characteristics nor functional outcomes.

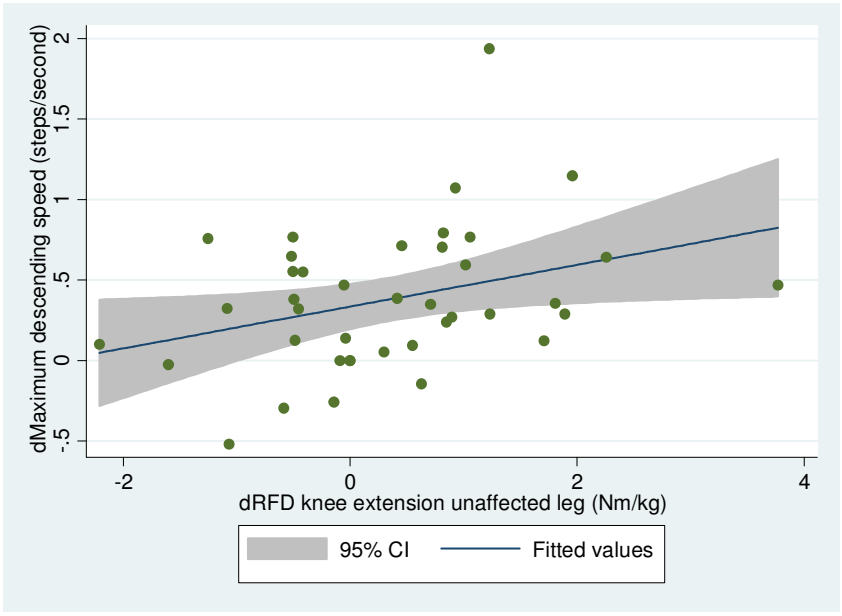
Figure 3

The associations between changes in isometric knee extension rate of force development (dRDF) and changes in descending stair walking speed (dDescending speed) following 10 weeks of explosive –type resistance training in affected leg (a) and unaffected leg (b).

a)



b)



Discussion

In this explorative randomized study we report on the preoperative effects of preoperative explosive RT on leg muscle strength, fat free mass and physical functioning compared to care as usual in hip OA patients, scheduled for THA. Despite numerous studies have shown association between symptomatic hip OA and impaired leg muscle strength and muscle atrophy [2,17,24–26], simultaneous measured muscle strength characteristics and muscle mass and their association with physical function have not been investigated in hip OA patients in relation to preoperative exercise interventions.

The primary finding of this study was that pre-operative explosive-type RT improved leg muscle strength in terms of maximal isometric muscle torque and explosive force characteristics (RFD) during single joint hip and knee extension compared to care as usual in hip OA patients scheduled for THA. Besides improvements in muscle strength, increases in total and regional (femoral) fat free mass and better physical functioning, reflected by faster stair negotiation, faster chair rise as well as faster horizontal gait speed, were observed.

Changes in maximal isometric muscle torque and explosive force characteristics of the knee extensors were associated with the improvements in physical function. The latter observation may be of relevance for targeting of intervention in future training regimens.

Preoperative explosive-type RT and muscle torque

Except one study (Gilbey et al, 2003) previous studies of preoperative exercise including strengthening exercises as an adjunct [9–12] have failed to provide evidence for the effect of exercise therapy on muscle function in hip OA patients scheduled for THA. This may be explained by insufficient intensity,

training volume/dose, progression, and/or compliance since only one study (Gilbey et al 2003) qualify for the definitions of progressive RT [13,27]. Gilbey et al, 2003 reported a significant between group differences in a combined leg muscle strength score after 8 weeks of slow velocity RT. Gilbey et al, 2003 does not report on objective physical functioning; however subgroup of participants was analyzed regarding physical functioning with no effect on walking speed (25 meters) prior to surgery[9]

In contrast, the present training protocol, based solely on preoperative explosive-type RT, resulted in significant between-group differences in maximal isometric muscle torque for knee and hip extension and physical functioning in favor of intervention (Table 2). In hip OA patients, explosive type RT have solely been investigated as a post-operative intervention[17,28–30]. Suetta et al (2004) reported explosive-type RT to be superior to conventional physiotherapy and neuromuscular electrical stimulation in the early rehabilitation phase, according to MVC, explosive force characteristics (RFD) and functional tasks [17]. The current improvement in leg muscle MVC in favor for intervention (15 %-22%), for the affected side appears slightly smaller than the finding by Suetta et al (2004) (+ 24%) which might be explained by a longer training period (12 weeks vs. 10 weeks) with a higher training volume (3 times/week vs. 2 times /week) and a different patient group [17]. Furthermore, impaired range of motion and/or pain, presumable present in hip OA patients scheduled for surgery, may theoretically account for a reduced training effect. However, we have previously investigated the feasibility of preoperative explosive-type RT in hip OA patients scheduled for THA and concluded that the training program was feasible (low exercise related pain) and followed by significant improvements in pain and self-evaluated function (data not yet published). However, as MVC improved equally between affected and unaffected leg, potential impaired joint function did not seem to affect the training effect for the present patient group.

Although the explosive force development in the initial phase of muscle contraction characterizes important aspects of the muscle function in relation to strenuous ADL tasks, such as stair climb and

prevention of falling[4], explosive force characteristics of leg muscles in terms of RFD has yet not been described in relation to preoperative exercise therapy.

The current training protocol was effective in improving explosive force characteristics (RFD 0-200ms) on the affected leg (Table 2). Surprisingly, the improvements in RFD were not retrieved on the unaffected leg. However, in a comparative study of explosive-type RT in 'very old' individuals (age (years); 81.8 ±SD 2.7) vs. 'old' (age (years); 62.7 ±SD 2.2), Caserotti et al (2008) described that relative RFD improvements were substantially larger in the physically more impaired 'very old' group [15]. Consequently, the affected leg may have been more responsive towards training than the non-affected leg. The present training effect on RFD may have been caused by improvements in neuromuscular activation (electromyogram (EMG) amplitude) [17]and/or hypertrophy of especially Type 2 muscle fibers as previously described in explosive-type RT performed after THA by Suetta et al[30] . However, it was beyond the limits of this explorative study to include measurements of EMG or muscle morphology

For both the affected and unaffected leg the average regional (femoral) muscle mass increased significantly following RT compared to controls, indicating training induced hypertrophy. The present gain in regional lean muscle mass (+2%) is relatively small compared with a larger (+5% to +12%) RT induced hypertrophy reported in healthy elderly and in hip OA patients after THA [17,31–33]. Consequently, the main part of the present improvement in muscle function is attributed to adaptations of the neural system rather than hypertrophy. However, differences between methods used for quantifying muscle hypertrophy may restrict the direct comparison between studies.

Effect on physical functioning and the correlation to muscle function and muscle mass

Physical functioning (horizontal gait, stair climb and sit-to-stand) was improved significantly in the intervention group compared to control at follow-up (Table 2). This have not previously been reported in studies of preoperative exercise therapy [9–12]. In healthy elderly, leg extension muscle function has been reported as a strong determinant for stair negotiation[4,34]. Thus, the lack of effect on physical functioning reported in previous studies of preoperative exercise therapy, most likely reflect unchanged muscle function. With increasing age, the functional reserve capacity declines, resulting in ADL functions are performed closer to the maximal capacity [14,35]. This process may accelerate in individuals with hip OA due to impairments in muscle function[1–3]. However, reserve capacity *per se* was not investigated in the current population but the present data holds promise for improved function, even in end stage OA.

Associations between training induced alterations in MVC and stair negotiation (ascending and descending) were only observed between MVC for knee extension (affected side) and improvements in stair negotiation speed (ascending and descending) (Figure 3), while changes in RFD (unaffected side) solely was associated to stair descending speed. Interestingly, Suetta et al observed changes in RFD to correlated with improved physical function (changes in maximum horizontal speed), while no correlation between increase in MVC and walking speed was observed[17]. Our findings indicate that optimizing stair negotiation in hip OA patients may rely on improvements in both maximal strength and explosive force of the knee extensors.

Clinical implications

In a clinical perspective augmenting leg muscle strength prior to surgery may be an important target of intervention as low muscle strength before surgery has been described as a predictor for poor

post-operative outcome according to ADL function [36]. This study indicates that muscle strength in hip OA patients scheduled for THA respond positively to explosive RT and the improvements are related to significant better physical functioning during a strenuous ADL task[37]. Only changes in MVC and explosive force characteristics of the knee extensors were associated with the improvements in physical functioning. Association between improvements in knee extension muscle torque and enhanced physical functioning were found in both legs. The latter observations may be of relevance for targeting of intervention in future regimens. Importantly, following the intervention, MVC and RFD outcomes of the affected leg leveled the baseline measurements of the unaffected leg (Table 2). Thus, the present data may indicate that 10 weeks of explosive-type RT prior to surgery has the potential to outlevel OA related deficits in muscle strength.

Limitations

Due to the 10 weeks of preoperative intervention in the intervention group, we allowed for patients in the control group to be operated according to the regular waiting list to apply high external validity. As a consequence surgery was delayed by 6 weeks in the intervention group due to a 1 month treatment guarantee provided by the Danish health care system. This discrepancy in time-to-surgery between groups represents a limitation regarding the internal validity, however a recent meta-analysis demonstrates strong evidence that (self reported) ADL function in hip OA patients do not deteriorate during waiting times (< 180 days) to THA [38]. Regarding changes in mechanical muscle function and physical functioning or muscle mass, little is known about the time course of preoperative deterioration as the evidence for preoperative impairment of these outcomes is entirely based on cross sectional studies[2,25,26]. However, the present findings suggest minor or no decline in mechanical muscle function and stable physical functioning in short term waiting for THA.

Assessor blinding of physical function and muscle strength was not possible to implement without violation, since logistics at the combined test and training site made sufficient masking impossible. To minimize assessor bias a standardized protocol for instruction and verbal encouragement was followed strictly during the collection of mechanic muscle outcomes and physical functioning. As only one assessor was used issues concerning inter-observer variability were avoided.

Conclusion

Intervention with explosive-type RT enhances preoperative maximal leg muscle torque and explosive force as well as physical functioning compared to care-as usual in hip OA patients scheduled for THA. Additionally, increased total and regional (femoral) fat free mass was observed following training, indicating more muscle mass. Associations between improvements of knee extension muscle function and stair negotiation in the intervention group indicates knee extension strength to be an important target for rehabilitation of physical function in hip OA. In perspectives, the result holds promise for a better postoperative outcome which will be further analyzed in a future study.

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